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Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia (Review)

Bergman H, Rathbone J, Agarwal V, Soares-Weiser K

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[Intervention Review]

Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia

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ABSTRACT

Background

Since the 1950s antipsychotic medication has been extensively used to treat people with chronic mental illnesses such as schizophrenia. These drugs, however, have also been associated with a wide range of adverse effects, including movement disorders such as tardive dyskinesia (TD) – a problem often seen as repetitive involuntary movements around the mouth and face. Various strategies have been examined to reduce a person's cumulative exposure to antipsychotics. These strategies include dose reduction, intermittent dosing strategies such as drug holidays, and antipsychotic cessation.

Objectives

To determine whether a reduction or cessation of antipsychotic drugs is associated with a reduction in TD for people with schizophrenia (or other chronic mental illnesses) who have existing TD. Our secondary objective was to determine whether the use of specific antipsychotics for similar groups of people could be a treatment for TD that was already established.

Search methods

We updated previous searches of Cochrane Schizophrenia's study-based Register of Trials including the registers of clinical trials (16 July 2015 and 26 April 2017). We searched references of all identified studies for further trial citations. We also contacted authors of trials for additional information.

Selection criteria

We included reports if they assessed people with schizophrenia or other chronic mental illnesses who had established antipsychotic-induced TD, and had been randomly allocated to (a) antipsychotic maintenance versus antipsychotic cessation (placebo or no intervention), (b) antipsychotic maintenance versus antipsychotic reduction (including intermittent strategies), (c) specific antipsychotics for the treatment of TD versus placebo or no intervention, and (d) specific antipsychotics versus other antipsychotics or versus any other drugs for the treatment of TD.

Data collection and analysis

We independently extracted data from these trials and estimated risk ratios (RR) or mean differences (MD), with 95% confidence intervals (CI). We assumed that people who dropped out had no improvement.

Main results

We included 13 RCTs with 711 participants; eight of these studies were newly included in this 2017 update. One trial is ongoing.

There was low-quality evidence of a clear difference on no clinically important improvement in TD favouring switch to risperidone compared with antipsychotic cessation (with placebo) (1 RCT, 42 people, RR 0.45 CI 0.23 to 0.89, low-quality evidence). Because evidence was of very low quality for antipsychotic dose reduction versus antipsychotic maintenance (2 RCTs, 17 people, RR 0.42 95% CI 0.17 to 1.04, very low-quality evidence), and for switch to a new antipsychotic versus switch to another new antipsychotic (5 comparisons, 5 RCTs, 140 people, no meta-analysis, effects for all comparisons equivocal), we are uncertain about these effects. There was low-quality evidence of a significant difference on extrapyramidal symptoms: use of antiparkinsonism medication favouring switch to quetiapine compared with switch to haloperidol (1 RCT, 45 people, RR 0.45 CI 0.21 to 0.96, low-quality evidence). There was no evidence of a difference for switch to risperidone or haloperidol compared with antipsychotic cessation (with placebo) (RR 1 RCT, 48 people, RR 2.08 95% CI 0.74 to 5.86, low-quality evidence) and switch to risperidone compared with switch to haloperidol (RR 1 RCT, 37 people, RR 0.68 95% CI 0.34 to 1.35, very low-quality evidence).

Trials also reported on secondary outcomes such as other TD symptom outcomes, other adverse events outcomes, mental state, and leaving the study early, but the quality of the evidence for all these outcomes was very low due mainly to small sample sizes, very wide 95% CIs, and risk of bias. No trials reported on social confidence, social inclusion, social networks, or personalised quality of life, outcomes that we designated as being important to patients.

Authors' conclusions

Limited data from small studies using antipsychotic reduction or specific antipsychotic drugs as treatments for TD did not provide any convincing evidence of the value of these approaches. There is a need for larger trials of a longer duration to fully investigate this area.

PLAIN LANGUAGE SUMMARY

Antipsychotic-reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia

Review question

To determine whether stopping or reducing antipsychotic drugs helps in the reduction of tardive dyskinesia for people with schizophrenia. To examine whether specific antipsychotic drugs could be a treatment for tardive dyskinesia.

Background

People with schizophrenia often hear voices and see things (hallucinations) and have strange beliefs (delusions). The main treatment for schizophrenia is antipsychotic drugs. However, these drugs can have debilitating side effects. Tardive dyskinesia is an involuntary movement that causes the face, mouth, tongue, and jaw to convulse, spasm, and grimace. It is caused by long-term use or high doses of antipsychotic drugs, is difficult to treat, and can be incurable. Various strategies have been proposed to reduce a person's exposure to antipsychotic drugs. These include lowering the dose of medication, intermittent 'drug holidays', and stopping taking antipsychotic medication altogether.

Study characteristics

The review includes 13 trials with a total of 711 people with schizophrenia and other psychiatric diagnoses.

Key results

Due to the poor quality, small size, and limited data from the 13 studies, there is limited evidence. It is not known if strategies such as dose reduction, 'drug holidays', and stopping medication are helpful in the treatment of tardive dyskinesia. There is limited evidence on specific antipsychotic drugs in the treatment of tardive dyskinesia.

Quality of the evidence

Evidence is poor, small scale, and of short duration. There is a need for larger trials of a longer duration in order to fully investigate this area.

This plain language summary was adapted by the review authors from a summary originally written by Ben Gray, Senior Peer Researcher, McPin Foundation (http://mcpin.org/).

Summary of findings for the main comparison. Reduced dose of antipsychotics compared with antipsychotic maintenance for antipsychotic-induced tardive dyskinesia

Reduced dose of antipsychotic compared with antipsychotic maintenance for antipsychotic-induced tardive dyskinesia

Patient or population: psychiatric patients (schizophrenia or schizoaffective disorder) with antipsychotic-induced tardive dyskinesia
Setting: inpatients and outpatients in the UK (1 study) and the USA (1 study)
Intervention: Reduced dose of antipsychotic
Comparison: Antipsychotic maintenance

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antipsychotic maintenance	Risk with reduced dose of antipsychotic				
Tardive dyskinesia: no clinically important improvement Follow-up: 44-48 weeks	Study population		RR 0.42 (0.17 to 1.04)	17 (2 RCTs)	⊕⊖⊖⊖ Very low[1,2]	
	875 per 1000	368 per 1000 (149 to 910)				
Tardive dyskinesia: deterioration of symptoms Follow-up: 44-48 weeks	Study population		RR 0.61 (0.11 to 3.31)	17 (2 RCTs)	⊕⊖⊖⊖ Very low[1,2]	
	250 per 1000	153 per 1000 (28 to 828)				
General mental state: relapse Follow-up: 44-48 weeks	Study population		RR 3.00 (0.16 to 57.36)	8 (1 RCT)	⊕⊖⊖⊖ Very low[2,3]	
	0 per 1000	0 per 1000 (0 to 0)				
Adverse effect: any - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Adverse effect: extrapyramidal symptoms - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.

Acceptability of the treatment: leaving the study early Follow-up: 44-48 weeks	Study population		RR 0.33 (0.06 to 1.99)	8 (1 RCT)	⊕⊖⊖⊖ Very low[2,3,4]	
	750 per 1000	248 per 1000 (45 to 1000)				
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for risk of bias: none of the studies adequately described allocation concealment, one study was a subsample from one site of an RCT, and one study's baseline characteristics were not balanced between study groups.
[2]Downgraded two levels for imprecision: 95% CI includes both no effect and appreciable benefit for antipsychotic reduced dose; very small sample size.
[3]Downgraded one level for risk of bias: allocation concealment was not adequately described, only a subsample from one site of an RCT qualified for inclusion.
[4]Downgraded one level for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 2. Antipsychotic cessation compared with antipsychotic maintenance for antipsychotic-induced tardive dyskinesia

Antipsychotic cessation compared with antipsychotic maintenance for antipsychotic-induced tardive dyskinesia

Patient or population: psychiatric patients with antipsychotic-induced tardive dyskinesia
Setting: inpatients and outpatients in any country
Intervention: Antipsychotic cessation
Comparison: Antipsychotic maintenance

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Antipsychotic maintenance	Antipsychotic cessation	

There is no evidence about the effects of withdrawal of antipsychotics compared with continuation of antipsychotics; none of the included studies evaluated this comparison.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Summary of findings 3. Switch to another antipsychotic compared with antipsychotic cessation for antipsychotic-induced tardive dyskinesia

Switch to another antipsychotic compared with antipsychotic cessation for antipsychotic-induced tardive dyskinesia

Patient or population: psychiatric patients (schizophrenia) with antipsychotic-induced tardive dyskinesia
Setting: inpatients in Canada (1 study) and Taiwan (1 study)
Intervention: Switch to another antipsychotic (risperidone, haloperidol)
Comparison: Antipsychotic cessation (with placebo; from FGAs)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antipsychotic cessation (placebo)	Risk with switch to another antipsychotic				
Tardive dyskinesia: no clinically important improvement Follow-up: 12 weeks	Study population		RR 0.45 (0.23 to 0.89)	42 (1 RCT)	⊕⊕⊖⊖ Low[1,2]	
	700 per 1000	315 per 1000 (161 to 623)				
Tardive dyskinesia: deterioration of symptoms - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.

General mental state: average endpoint score (BPRS, high = poor) Follow-up: 12 weeks	The mean general mental state average endpoint score (BPRS, high = poor) was 19	MD 4.30 lower (10.48 lower to 1.88 higher)	-	42 (1 RCT)	⊕⊖⊖⊖ Very low[1,3]	
Adverse effect: any - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Adverse effects: use of antiparkinsonism drugs Follow-up: 8-12 weeks	Study population 273 per 1000	567 per 1000 (202 to 1000)	RR 2.08 (0.74 to 5.86)	48 (1 RCT) [4]	⊕⊖⊖⊖ Very low[1,3]	Another study reported ESRS scale data for parkinsonism and also found little or no difference between groups (MD -0.4 95% CI -1.25 to 0.45, 42 participants).
Acceptability of the treatment: leaving the study early Follow-up: 12 weeks	Study population 200 per 1000	120 per 1000 (32 to 450)	RR 0.60 (0.16 to 2.25)	50 (1 RCT)	⊕⊖⊖⊖ Very low[1,3,5]	
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **FGA:** first-generation antipsychotic; **MD**: mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for risk of bias: generation of random sequence and allocation concealment not adequately described.
[2] Downgraded one level for imprecision: very small sample size.
[3] Downgraded two levels for imprecision: 95% CI includes appreciable benefit for both interventions as well as no effect; very small sample size.
[4] Two comparisons from one study.
[5] Downgraded one level for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 4. Switch to a specific antipsychotic compared with switch to a different specific antipsychotic for antipsychotic-induced tardive dyskinesia

Switch to specific antipsychotic compared with switch to a different specific antipsychotic for antipsychotic-induced tardive dyskinesia

Patient or population: psychiatric patients (mainly schizophrenia) with antipsychotic-induced tardive dyskinesia
Setting: inpatients and outpatients in Canada (1 study), Denmark and Finland (1 study), South Africa (1 study), Taiwan (2 studies) and the USA (5 studies)
Interventions: switch to specific antipsychotic (amisulpride, clozapine, haloperidol, molindone, olanzapine, risperidone, thiopropazate, quetiapine, ziprasidone, zuclopenthixol)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with specific antipsychotic 1	Risk with specific antipsychotic 2				
Tardive dyskinesia: no clinically important improvement Follow-up: 3-50 weeks	Study population See comment	See comment	-	140 (4 RCTs)	⊕⊖⊖⊖ Very low[1,2]	No meta-analysis, studies stratified by antipsychotic. The following comparisons found no clinically important improvement: THI vs HAL, ZUC vs HAL, OLZ vs RIS, QUE vs HAL
Tardive dyskinesia: deterioration Follow-up: 3-4 weeks	Study population See comment	See comment	-	35 (2 RCTs)	⊕⊖⊖⊖ Very low[1,2]	No meta-analysis, studies stratified by antipsychotic. The following comparisons found no difference in deterioration: THI vs HAL, ZUC vs HAL
General mental state: deterioration Follow-up: 3-50 weeks	Study population See comment	See comment	-	120 (3 RCTs)	⊕⊖⊖⊖ Very low [1,2]	No meta-analysis, studies stratified by antipsychotic. The following comparisons found no difference in mental state deterioration: ZUC vs HAL, OLZ vs RIS, QUE vs HAL
Adverse events: extrapyramidal symptoms (need of antiparkinsonism drugs) Follow-up: 8-50 weeks	Study population See comment	See comment	-	53 (2 RCTs)	⊕⊕⊖⊖ Low[1,3]	No meta-analysis, studies stratified by antipsychotic. HAL more likely to need antiparkinsonism drugs than QUE (1 RCT, 45 participants, RR 0.45, 95% CI 0.21 to 0.96). No difference: RIS vs HAL
Adverse effects: general adverse events (UKU Average change score)	See comment	See comment	-	80 (1 RCT)	⊕⊖⊖⊖ Very low[1,2]	No meta-analysis, 3-arm study comparing OLZ, ASP and unspecified FGAs found no difference in general adverse events for all pairwise comparisons.

Follow-up: 24 weeks						
Acceptability of the treatment: leaving the study early Follow-up: 2 weeks - 18 months	Study population		-	466 (7 RCTs)	⊕⊖⊖⊖ Very low[1,2,4]	RIS more likely to leave study early than OLZ (2 RCTs, 130 participants, RR 0.73, 95% CI 0.57 to 0.95). Remaining studies no meta-analysis, no difference (6 RCTs, 450 participants): MOL/THI/CLO/QUE vs HAL, OLZ/ASP vs unspecified FGAs, OLZ vs QUE/ZIP, QUE vs ZIP/RIS, ZIP vs RIS
	See comment	See comment				
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	None of the included studies reported on this outcome.					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ASP: amisulpride; **CI:** confidence interval; **CLO:** clozapine; **FGA:** first-generation anti-psychotic; **HAL:** haloperidol; **MOL:** molindone; **OLZ:** olanzapine; **RCT:** randomised controlled trial; **RIS:** risperidone; **RR:** risk ratio; **THI:** thiopropazate; **QUE:** quetiapine; **ZIP:** ziprasidone; **ZUC:** zuclopenthixol

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one step for risk of bias: randomisation procedure, allocation concealment or blinding were not adequately described.
[2]Downgraded two steps for imprecision: small sample size, and 95% CI includes appreciable benefit for both or one of the interventions as well as no effect.
[3]Downgraded one step for imprecision: small sample size.
[4]Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 5. Specific antipsychotic compared with other drugs for antipsychotic-induced tardive dyskinesia

Specific antipsychotic compared with other drugs for antipsychotic-induced tardive dyskinesia

Patient or population: psychiatric patients (mainly schizophrenia) with antipsychotic-induced tardive dyskinesia
Setting: inpatients in the USA (1 study)
Intervention: specific antipsychotic (haloperidol)
Comparison: other drugs (tetrabenazine)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with tetrabenazine	Risk with haloperidol				
Tardive dyskinesia: not improved to a clinically important extent Follow-up: 18 weeks	Study population		RR 1.07 (0.51 to 2.23)	13 (1 RCT)	⊕⊖⊖⊖ Very low[1,2]	
	667 per 1000	713 per 1000 (340 to 1000)				
Tardive dyskinesia: deterioration of symptoms Follow-up: 18 weeks	Study population		RR 0.86 (0.07 to 10.96)	13 (1 RCT)	⊕⊖⊖⊖ Very low[1,2]	
	167 per 1000	143 per 1000 (12 to 1000)				
Mental state - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Adverse effect: any - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Adverse effect: extrapyramidal symptoms - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Acceptability of the treatment: leaving the study early Follow-up: 18 weeks	Study population		RR 4.38 (0.25 to 76.54)	13 (1 RCT)	⊕⊖⊖⊖ Very low[1,2,3]	
	0 per 1000	0 per 1000 (0 to 0)				
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	See comment	See comment	Not estimable	(0 studies)	-	None of the included studies reported on this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __RCT:__ randomised controlled trial; __RR:__ risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

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[1]Downgraded one step for risk of bias: randomisation procedure, allocation concealment and blinding were not adequately described.
[2]Downgraded two steps for imprecision: small sample size, and 95% CI includes appreciable benefit for both interventions.
[3]Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

BACKGROUND

Description of the condition

Since the 1950s antipsychotic (neuroleptic) medication has been extensively used to treat people with chronic mental illnesses such as schizophrenia. These drugs can effectively control symptoms such as abnormal perceptions (hallucinations), disordered thinking, and fixed false beliefs (delusions). In addition, maintenance therapy with antipsychotic medication is associated with reduced risk of relapse (Schooler 1993). Antipsychotic medication, however, has also been associated with a wide range of adverse effects, including movement disorders. The appearance of these disorders can be extremely disfiguring, compounds stigma, and is associated with poor compliance to antipsychotic treatment (Barnes 1993; Tarsy 2011).

Tardive dyskinesia (TD) is one such iatrogenic movement disorder and it is characterised by abnormal repetitive and involuntary movements. The clinical features include: tongue protrusion, side-to-side or rotatory movement of the jaw, lip smacking, puckering and pursing, and rapid eye blinking (Casey 1999). In some people rapid movements of the arms, legs, and trunk may also occur. TD is a chronic condition of insidious onset, the severity of which fluctuates spontaneously (APA 1992). Although the most frequent cause of TD is the use of antipsychotic medication, it is striking that dose reduction can lead to a temporary exacerbation in symptoms. Conversely, increasing the dose is often associated with a temporary remission (Cavallaro 1993; Smith 1980).

The exact mechanisms of the pathophysiology of TD are unknown. Antipsychotic drugs block certain chemical receptor sites in the brain - one of these is specific for dopamine (Casey 1994). One hypothesis explaining the cause of antipsychotic-induced TD is that chronic blockade of dopamine receptors in specific cells of the brain (neurones from the nigrostriatum) causes an overgrowth of these receptors (Casey 1994). However, there is some suggestion that the chronic use of antipsychotics may also cause an abnormal production of highly active atoms and chemical groups (cytotoxic free radicals), which may damage specific cells in the brain. This, in turn, could be responsible for the appearance of TD (Cadet 1989). This theory is supported by the persistent nature of the syndrome, once established.

Studies on the natural history of TD have reported widely variable remission rates (1% to 62%) depending on patient age, psychiatric diagnosis, course of the psychiatric disorder, and duration of therapy (Bergen 1989; Fernandez 2001; Glazer 1990). TD occurs in more than 20% of people that use first-generation antipsychotic drugs (FGAs) continually for longer than three months (Tarsy 2011). Every year 4% to 5% of adults and 25% to 30% of elderly people who continually use these drugs begin to show signs of TD (APA 1992; Correll 2004). Advancing age is a risk factor for both TD's prevalence and severity, with those who are under 60 years of age being three times more likely to spontaneously remit (Smith 1980).

When the second-generation antipsychotic drugs were introduced in the 1990s many hoped that they would not cause TD (Miller 2007; Rosenheck 2007). Although the risk of developing TD with second-generation antipsychotic drugs does seem to be reduced, TD risks have not been eliminated (Miller 2007; Tarsy 2011). There is even some evidence to indicate that rates of TD do not differ at all between first- and second-generation anti-psychotic drugs (Leucht 2009; Rosenheck 2007; Woods 2010). The large, definitive, US randomised trial of antipsychotic treatments for schizophrenia (CATIE), with a four-year period of follow-up, obtained an incidence rate of TD of around 17% (Miller 2008). Due to widespread use of second-generation antipsychotic drugs, increased off-label use, and an ageing population, the frequency of TD is likely to be higher than thought (Cloud 2014; Maher 2012) and increasing. The problem will be considerably greater for people in countries where use of newer drugs is less prevalent (Ballesteros 2000; Martins 2011).

Description of the intervention

Various strategies have been examined in order to reduce a person's cumulative exposure to antipsychotics. These strategies include dose reduction, intermittent dosing strategies, such as drug holidays, and antipsychotic cessation. The prevention and treatment of TD provided much of the impetus for these studies. While antipsychotic reduction or cessation, or both would seem to be a logical first step in the management of antipsychotic-induced TD, this is not always possible in the clinical setting because of the overriding need to manage current psychotic symptoms or to reduce the risk of relapse, or both. In this review we undertook a comprehensive study of the impact of antipsychotic dose reduction and/or cessation strategies for those who were already presenting with TD.

In the search for ways to manage antipsychotic-induced TD, certain antipsychotic medications have themselves been proposed as specific treatments for the condition. The usual rationale for such trials relates to variations in receptor-blocking profile that distinguishes the compound of interest from antipsychotics in general.

How the intervention might work

Although the pathophysiology of TD is not entirely clear, one of the possible underlying mechanisms is believed to be hypersensitivity of postsynaptic dopamine receptors (Margolese 2005). The risk appears to increase with higher cumulative exposure to antipsychotics, especially those with stronger D2 dopamine receptor blockade. Newer antipsychotic medications, which cause less dopamine D2 blockade, have been shown to cause less TD (Correll 2004). The primary intervention of interest (reduction/cessation of antipsychotics), is likely to help by reducing the cumulative exposure to antipsychotics. The other intervention (specific antipsychotics) is likely to work as a result of the reduction in the levels of dopamine D2 receptor blockade, a characteristic property of many of the newer antipsychotic medications.

Why it is important to do this review

TD can result in considerable social and physical disability (Barnes 1993) and symptoms are often irreversible (Bergen 1989; Fernandez 2001; Gerlach 1988; Glazer 1990). Additionally, TD is frequently associated with lower quality of life (Ascher-Svanum 2008) and a greater mortality rate (Chong 2009). Several antipsychotic medications have been produced in recent decades that claim to cause less or no TD (Lieberman 1996). These claims may or may not be true, and certainly evidence does suggest that thoughtful use of older generation drugs is not associated with more TD than newer treatments (Chouinard 2008). However, in a global context, it is likely that the less expensive and more familiar drugs - such as chlorpromazine or haloperidol - will continue to be the mainstay of

treatment of people with schizophrenia (WHO Essential List 2010). Use of drugs such as these is associated with emergence of TD and, therefore, this condition will remain a problem for years to come.

Given the high incidence and prevalence of TD among people taking antipsychotic medication, the need for prevention or treatment is clear. Unfortunately, there has been sparse evidence to guide clinicians (NICE 2014; Taylor 2009). Although many treatments have been tested, no one intervention has been shown clearly to be effective.

This review is one in a series of Cochrane Reviews (see Table 1) evaluating treatments for antipsychotic-induced TD, and is an update of a Cochrane Review first published in 1998 (McGrath 1998), and previously updated in 2000 (McGrath 2000) and in 2006 (Soares-Weiser 2006).

OBJECTIVES

To determine whether a reduction or cessation of antipsychotic drugs is associated with a reduction in TD for people with schizophrenia (or other chronic mental illnesses) who have existing TD. Our secondary objective was to determine whether the use of specific antipsychotics for similar groups of people could be a treatment for already established TD.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. Had there been trials that were described as double-blind, but that did not mention whether the study was randomised, we would have included them in a sensitivity analysis. If there had been no substantive difference within primary outcomes (see 'Types of outcome measures') when these studies were added, then we would have included them in the final analysis. If there had been a substantive difference, we would have used only clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

We included people with schizophrenia or any other serious mental illness, diagnosed by any criteria, irrespective of gender, age, or nationality who required the use of antipsychotics for more than three months and who developed TD (diagnosed by any criteria) during antipsychotic treatment, and for whom the dose of antipsychotic medication had been stable for one month or more. We made a post hoc change to include studies that did not require antipsychotic medication to have been stable for one month prior to randomisation. We felt it important to include these studies as they provide additional important information. However, we planned to analyse these separately, so that they would not change existing outcome data.

Types of interventions

1. Reduction or cessation of the dose of antipsychotic drugs compared with the continuation of standard dose of the same compound. For the purposes of this review, we divided these trials into those that aimed to reduce the total dosage of antipsychotic medication, for example reduced-dose and intermittent-dosage schedule studies, and those that ceased antipsychotics (sometimes after variable periods of dose reduction).
2. Specific antipsychotic drugs proposed to have TD-lessening qualities compared with placebo or no intervention. We made a decision post hoc to broaden this criteria to also include antipsychotic versus antipsychotic and antipsychotic versus other drugs for the treatment of TD.

Types of outcome measures

We have defined clinical efficacy as an improvement in the symptoms of TD of more than 50%, on any scale. We grouped outcomes into short term (less than six weeks), medium term (between six weeks and six months) and long term (more than six months).

Primary outcomes

1. Tardive dyskinesia (TD) symptoms

No clinically important improvement in the symptoms of individuals, defined as more than 50% improvement on any TD scale - any time period.

2. Adverse effects

No clinically significant extrapyramidal adverse effects - any time period.

Secondary outcomes

1. Tardive dyskinesia (TD) symptoms

1.1 Any improvement in the symptoms of individuals on any TD scale, as opposed to no improvement
1.2 Deterioration in the symptoms of individuals, defined as any deleterious change on any TD scale
1.3 Average change in severity of TD during the trial period
1.4 Average difference in severity of TD at the end of the trial

2. General mental state changes

2.1 The number of people per treatment group who were defined as relapsed (according to any definition)
2.2 Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale
2.3 Average difference in severity of psychiatric symptoms at the end of the trial

3. Acceptability of the treatment

3.1 Acceptability of the intervention to the participant group as measured by numbers of people leaving the study early (dropping out) during the trial.

4. Adverse effects

4.1 The number of people per treatment group who had any adverse effect (other than deterioration of symptoms of TD or relapse).
4.2 Use of any antiparkinsonism drugs
4.3 Average score/change in extrapyramidal adverse effects
4.4 Acute dystonia

5. Other adverse effects, general and specific

6. Hospital and service utilisation outcomes

6.1 Hospital admission
6.2 Average change in days in hospital
6.3 Improvement in hospital status (for example: change from formal to informal admission status, use of seclusion, level of observation)

7. Economic outcomes

7.1 Average change in total cost of medical and mental health care
7.2 Total indirect and direct costs

8. Social confidence, social inclusion, social networks, or personalised quality-of-life measures

8.1. No significant change in social confidence, social inclusion, social networks, or personalised quality-of-life measures
8.2 Average score/change in social confidence, social inclusion, social networks, or personalised quality-of-life measures

9. Behaviour

9.1 Clinically significant agitation
9.2 Use of adjunctive medication for sedation
9.3 Aggression to self or others

10. Cognitive state

10.1 No clinically important change
10.2 No change, general and specific

In Effects of interventions we reported on all TD symptom outcomes grouped together and all adverse effects outomes grouped together, whether or not they were primary or secondary, and we indicated primary outcomes with a '*'.

'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011) and used GRADEpro to export data from this review to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from the included studies in the comparison, the magnitude of effects of interventions examined, and the sum of available data on all outcomes rated as important to patient care and decision making. We selected the following main outcomes for inclusion in the 'Summary of findings' table:

1. Tardive dyskinesia
1.1 Improved to a clinically important extent
1.2 Deteriorated

2. Mental state

3. Adverse effect
3.1 Any adverse event
3.2 Adverse effects: no clinically significant extrapyramidal adverse effects

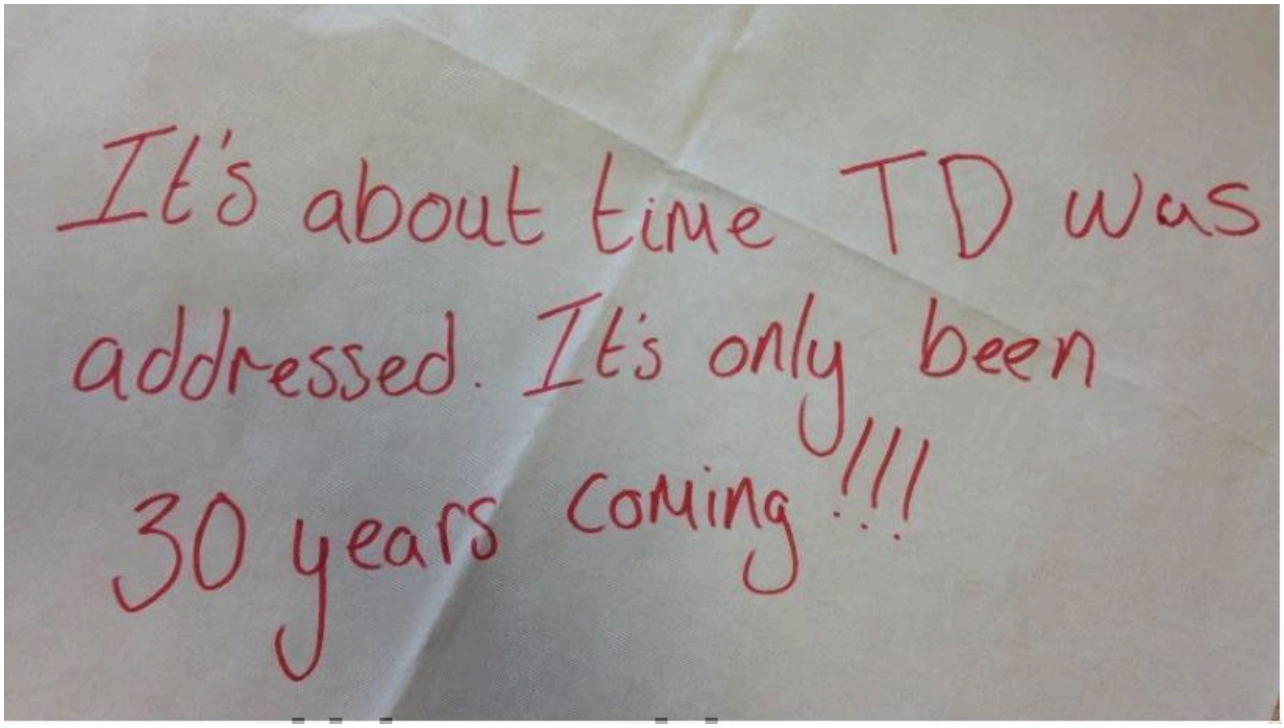
4. Acceptability of treatment
4.1 Leaving the study early

5. Social confidence, social inclusion, social networks, or personalised quality of-life-measures
5.1 No significant change in social confidence, social inclusion, social networks, or personalised quality-of-life measures for either recipients of care or caregivers

We used this summary to guide our conclusions.

Personalised quality-of-life is an outcome designated important to patients. We wished to add perspectives from people's personal experience with TD to the research agenda. We planned a consultation with service users, where the previously published version of a review in the Cochrane TD series (Soares-Weiser 2011; Table 1) and a lay overview of that review gave the foundation for the discussions. The session was planned to provide time to reflect on current research on TD and to consider gaps in knowledge. The report is published in the Health Technology Assessment (HTA) report for the UK National Institute of Health Research (Bergman 2017). We have added one figure showing one service user's expression of frustration concerning this neglected area of research (Figure 1). Informed by the results of the consultation, for this review, we have included outcomes of the consultation in the 'Summary of findings' tables.

Figure 1. Message from one of the participants of the public and patient involvement consultation of service user perspectives on tardive dyskinesia research



Search methods for identification of studies

Electronic searches

The 2017 review update was carried out in parallel with updating eight other Cochrane TD Reviews and the search covered all nine reviews; see Table 1 for details.

1. Cochrane Schizophrenia Group's Study-Based Register of Trials

On July 16, 2015 and April 26, 2017, the Information Specialist searched the register using the following string:

Tardive Dyskinesia in Healthcare Condition Field of Study

In a study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017).

This register is compiled by systematic searches of major resources (AMED, BIOSIS, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, hand-searches, grey literature, and conference proceedings (see Group's Module). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

For previous searches, please see Appendix 1.

Searching other resources

1. Reference searching

We inspected references of all identified studies for further relevant studies.

2. Personal contact

We contacted the first author of each included study for information regarding unpublished trials.

Data collection and analysis

Selection of studies

For the 2017 update, reviewers RA and AG (see Acknowledgements) inspected all abstracts of studies identified as above and identified potentially relevant reports. We resolved disagreement by discussion, or where there was still doubt, we acquired the full article for further inspection. We acquired the full articles of relevant reports/abstracts meeting initial criteria for reassessment and carefully inspected for a final decision on inclusion (see Criteria for considering studies for this review). RA and AG were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked review author HB for help and where it was impossible to decide or if adequate information was not available to make a decision, we added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

For the 2017 update, reviewers RA and HB independently extracted data from all included studies. Again, we discussed any disagreement and documented decisions. We extracted data presented only in graphs and figures whenever possible, but we included data only if two review authors independently had the same result. We attempted to contact study authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies were multi-centre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

For the 2017 update we extracted data online in Covidence. Extracted data are available here with a link to the original source PDF for each item.

2.2 Scale-derived data

We included continuous data from rating scales only if:

a) the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000); and
b) the measuring instrument had not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either have been (a) a self-report or (b) completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly, and we noted in Description of studies if this was the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. We decided to primarily use endpoint data, and only to use change data if the former were not available. We combined endpoint and change data in the analysis as we preferred to use mean differences (MD) rather than standardised mean differences throughout (Higgins 2011a).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant data before inclusion.

Please note, we entered data from studies of at least 200 participants in the analysis because skewed data pose less of a problem in large studies. We also entered all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not.

For endpoint data from studies with fewer than 200 participants:

(a) for scales starting from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation. If this value was lower than 1, it strongly suggested a skew and we excluded these data. If this ratio was higher than one but below 2, there was suggestion of skew. We entered these data and tested whether their inclusion or exclusion changed the results substantially. Finally, if the ratio was larger than 2 we included these data, because skew was less likely (Altman 1996; Higgins 2011a).

(b) for scales starting from a positive value (such as the Positive and Negative Syndrome Scale (PANSS, Kay 1986), which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and 'S min' is the minimum score.

2.5 Common measure

Where relevant, to facilitate comparison between trials, we converted variables that can be reported in different metrics, such as days in hospital (mean days per year, per week, or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we converted continuous outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the PANSS (Kay 1986), this can be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds were not available, we used the primary cut-off presented by the study authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for reduction or cessation of antipsychotic. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not un-improved') we presented data where the left of the line indicated an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

RA (see Acknowledgements) and HB independently assessed risk of bias within the included studies by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011b). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

If the raters disagreed, we made the final rating by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain further information. If non-concurrence occurred, we reported this.

We noted the level of risk of bias in the text of the review and in Figure 2; Figure 3 and 'Summary of findings' tables.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

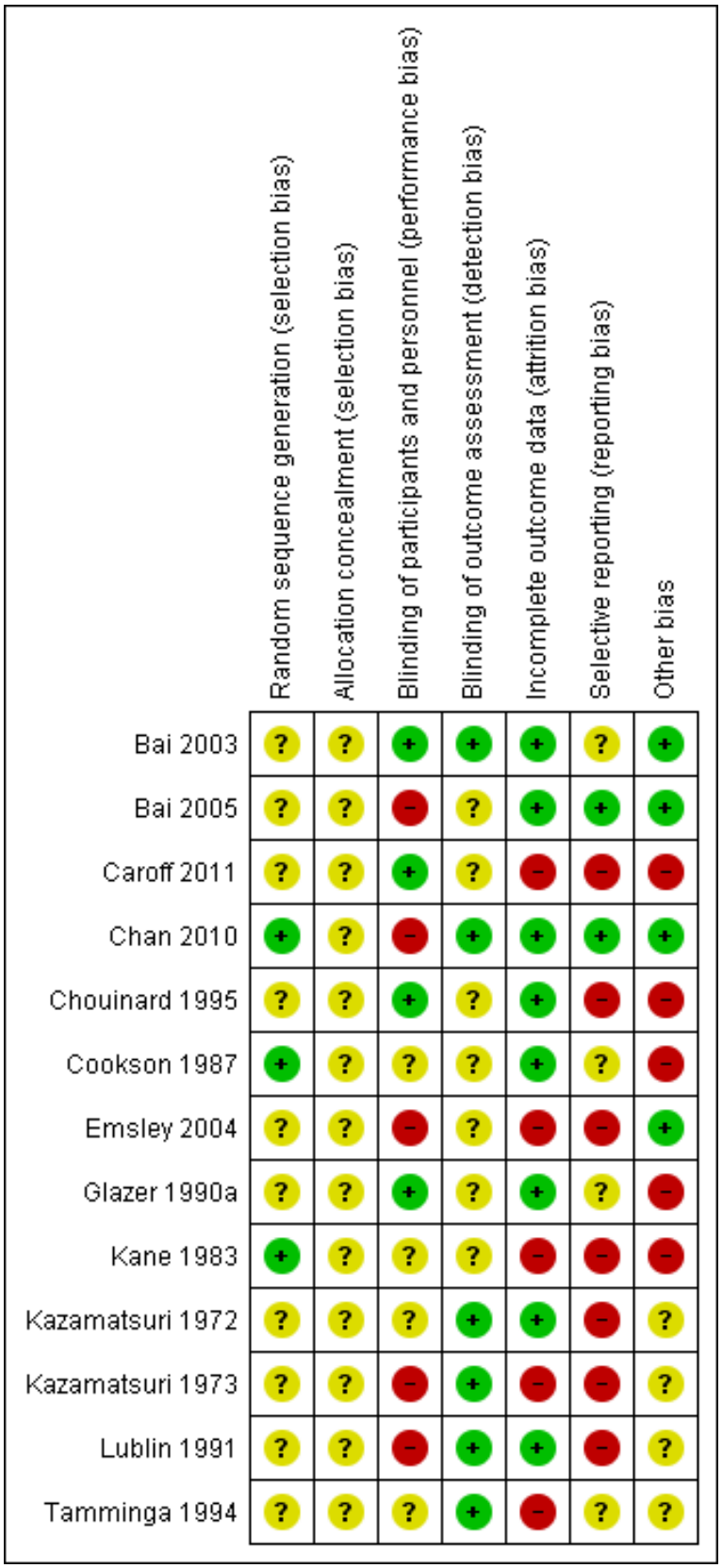
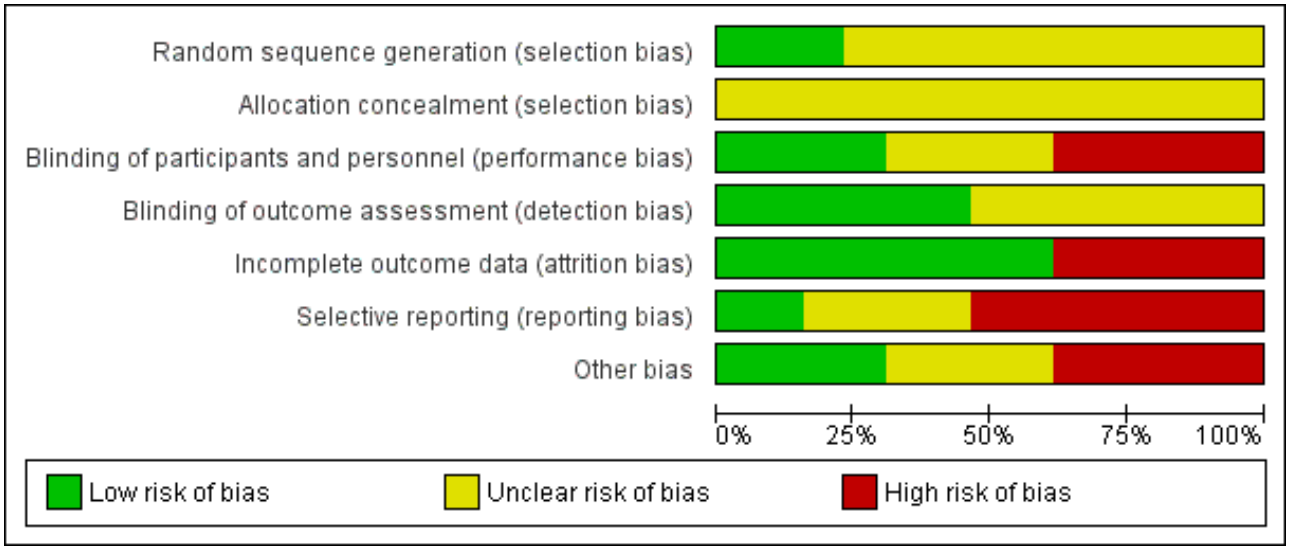


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios, as odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity were used, we presumed there was a small difference in measurement, and calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster-randomised trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, study authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow, and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

If any of the included trials had randomised participants by clusters, and where clustering was not accounted for in primary studies, we would have presented such data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, we presented these data as if from a non-cluster-randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) (design effect=1+(m-1)*ICC) (Donner 2002). If the ICC was not reported we would assume it was 0.1 (Ukoumunne 1999).

If cluster studies were appropriately analysed, taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. The carry-over effect occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a washout phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we only used data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data were binary we simply added and combined within the two-by-two table. If data were continuous we combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We did not use data where the additional treatment arms were not relevant.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We decided that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we addressed this within the 'Summary of findings' tables by down-rating quality. We also downgraded quality within the 'Summary of findings' tables should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50%, and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). We assumed that all those leaving the study early had seen no improvement in TD symptoms. We undertook a sensitivity analysis, testing how prone the primary outcomes were to change by comparing data only from people who had completed the study to that point to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We reported and used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who had completed the study to that point were reported.

3.2 Standard deviations

If standard deviations were not reported, we first tried to obtain the missing values from the study authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error and confidence intervals available for group means, and either P value or 't' value available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011c). When only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011a; Higgins 2011c) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges, or other statistics. If these formulae did not apply, we calculated the SDs according to a validated imputation method which was based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently, methods such as multiple imputation or mixed effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We therefore did not exclude studies based on the statistical approach used. However, we preferred to use the more sophisticated approaches (e.g. MMRM or multiple-imputation) and only presented completer analyses if some kind of ITT data were not available at all. Moreover, we addressed this issue in the item "incomplete outcome data" of the risk of bias tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations that we had not predicted would arise and discussed in the text if they arose.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods that we had not predicted would arise and discussed in the text if they arose.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 statistic method alongside the Chi^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 statistic depends on (a) magnitude and direction of effects and (b) strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2 statistic). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic can be interpreted as evidence of substantial levels of heterogeneity (section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions* Deeks 2011). We explored and discussed in the text potential reasons for substantial levels of heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were ten or fewer studies, or where all studies were of similar sizes. In future versions of this review, if funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose the fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We anticipated one subgroup analysis to test the hypothesis that the use of antipsychotic reduction, cessation or specific antipsychotics is most effective for those with early-onset TD (less than five years). We hoped to present data for this subgroup for the primary outcomes.

1.2 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of antipsychotic reduction/cessation or specific antipsychotics for people with TD in general. In addition, however, we tried to report data on subgroups of people in the same clinical state, stage, and with similar problems.

2. Investigation of heterogeneity

We reported that inconsistency was high. First, we investigated whether data were entered correctly. Second, if data were correct, we visually inspected the graph and successively removed studies outside of the company of the rest to see if homogeneity was restored. For this review we decided that, should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present the data. If not, we did not pool such data and discussed issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity were obvious, we simply discussed. We did not undertake sensitivity analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

If trials were described in some way as to imply randomisation we undertook a sensitivity analysis for the primary outcomes. We included these studies in the analyses, and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, we used relevant data from these studies.

2. Assumptions for lost binary data

Where we had to make assumptions regarding people lost to follow-up (see Dealing with missing data) we compared the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we reported and discussed these results but continued to employ our assumption.

Where we had to make assumptions regarding missing SD data (see Dealing with missing data), we compared the findings on primary outcomes when we used our assumption compared with completer data only. We undertook a sensitivity analysis, testing how prone results were to change when completer data only were compared with the imputed data using the above assumption. If there was a substantial difference, we reported and discussed these results but continued to employ our assumption.

3. Risk of bias

We analysed the effects of excluding trials that we judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available) allocation concealment, blinding, and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, we included data from these trials in the analysis

4. Imputed values

Had cluster-randomised trials been included, we would have undertaken a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect.

If we found substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately

5. Fixed-effect and random-effects models

We synthesised data using a fixed-effect model; however, we also synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of the results.

RESULTS

Description of studies

Please see Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies.

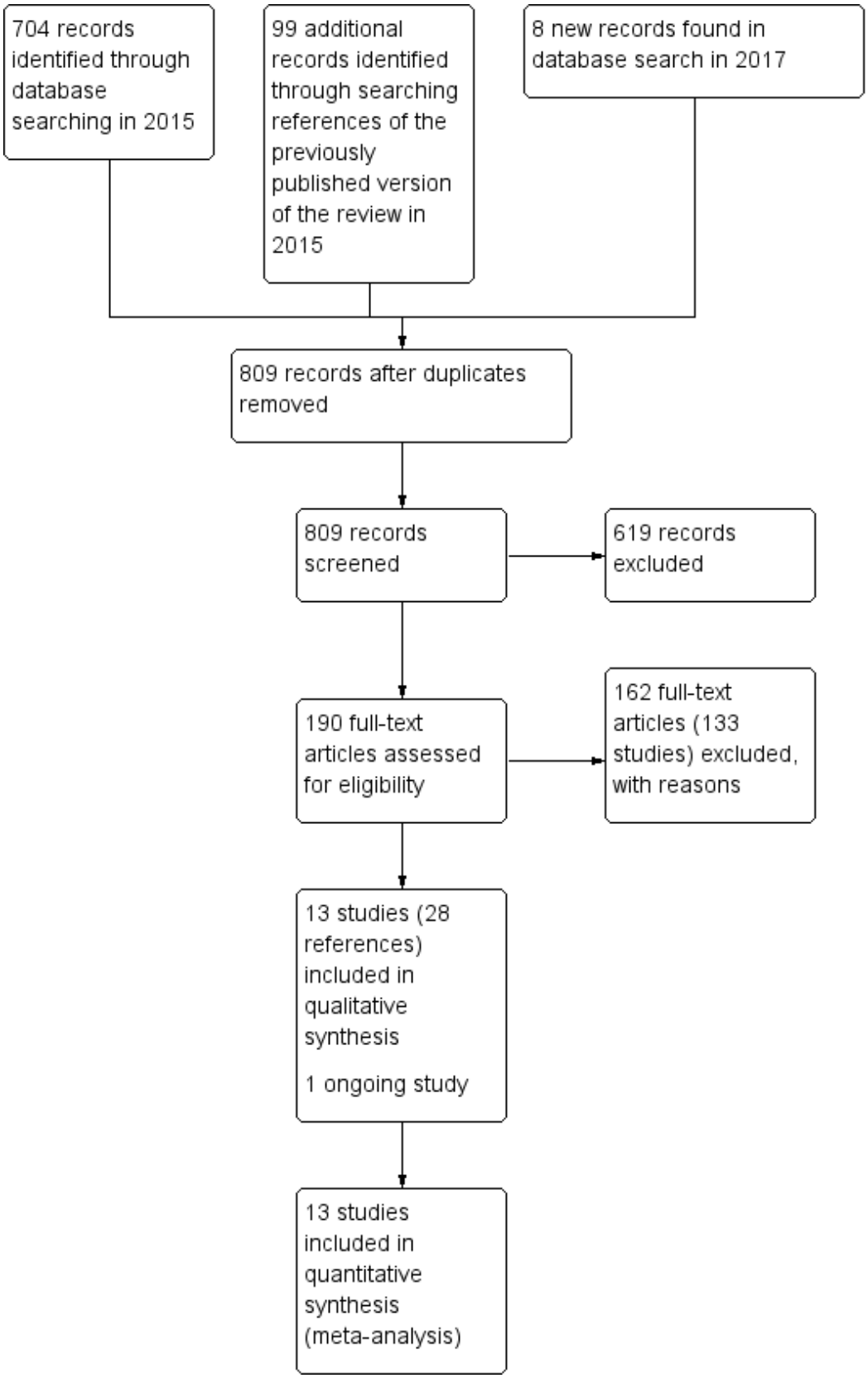
Results of the search

The 2015 and 2017 searches for the 2017 review update also covered updates for the other eight Cochrane Reviews in the TD series, see Table 1.

The 2015 search retrieved 704 references for 344 studies, see Figure 4 for study flow diagram (Moher 2009). We also screened all references of the previously published review, 99 of which were not covered in the updated search. We identified 18 new potentially relevant studies for this review for which we conducted full-text screenings. Five of these studies are newly included in this review (Bai 2005; Caroff 2011; Chan 2010; Chouinard 1995; Kazamatsuri 1973). A study previously awaiting classification was included as several more publications were identified in the new search (Bai 2003). Two studies were previously excluded because there was no

placebo group, but as head-to-head comparisons of antipsychotic drugs for the treatment of TD has been added to the inclusion criteria in this review, these studies were subsequently included (Lublin 1991; Tamminga 1994). We also added 13 new excluded studies, and three studies previously awaiting classification were also excluded (Barnes 2002; Cai 1988; Zeng 1994).

Figure 4. Study flow diagram for 2015 and 2017 searches for this review



The 2017 search found 8 records (5 studies). Editorial base of Cochrane Schizophrenia screened these records and no new studies were relevant to this review. They could be relevant to the other reviews in this series of TD reviews (see Table 1), and have been put into awaiting assessment of the Miscellaneous treatments review Soares-Weiser 2006 and the benzodiazepines review Bhoopathi 2006.

Thirteen studies are now included in this review (Tamminga 1994; Cookson 1987; Kane 1983; Kazamatsuri 1973; Glazer 1990a; Bai 2005; Caroff 2011; Chan 2010; Emsley 2004; Chouinard 1995; Bai 2003; Kazamatsuri 1972; Lublin 1991).

Included studies

Overall the review now includes 13 studies with 711 participants published between 1972 and 2011.

1. Methods

Most studies stated that they were randomised and double-blind. Two studies reported being only single-blind (Bai 2005; Chan 2010). For further details please see sections below on allocation and blinding.

2. Design

All included studies presented a parallel longitudinal design. One of the 13 studies used a cross-over design with two periods (Lublin 1991). We had considered this as likely when embarking on the review and have used only the data from before the first cross-over for the reasons outlined above (Unit of analysis issues).

3. Duration

We included three short-term studies reporting data at two to four weeks (Glazer 1990a; Kazamatsuri 1972; Lublin 1991). Five studies reported data at medium-term, 8 to 24 weeks (Bai 2003; Bai 2005; Chan 2010; Chouinard 1995; Kazamatsuri 1973), and there were five long-term studies reporting data at 44 weeks to 18 months (Caroff 2011; Cookson 1987; Emsley 2004; Kane 1983; Tamminga 1994).

4. Participants

Participants, now totaling 711 people, were mostly men with aged 50 to 60 years with diagnoses of various chronic psychiatric disorders, but mainly schizophrenia. All had antipsychotic-induced TD diagnosed using Schooler and Kane's research diagnostic criteria, except Lublin 1991, which did not report any criteria for the diagnosis of TD. The number of participants ranged from 8 to 200 (median 32).

5. Setting

Most trials were conducted in hospital. The studies themselves were from around the world, with six conducted in the USA (Caroff 2011; Glazer 1990a; Kane 1983; Kazamatsuri 1972; Kazamatsuri 1973; Tamminga 1994), three in Taiwan (Bai 2003; Bai 2005; Chan 2010), and one each in South Africa (Emsley 2004), Canada (Chouinard 1995), Denmark/Finland (Lublin 1991), and the UK (Cookson 1987).

6. Interventions

6.1 Antipsychotic reduction

6.1.1 cis(z)-flupenthixol decanoate

Cookson 1987 used a reduction of 50% of the standard dose of cis(z)-flupenthixol decanoate.

6.1.2 Fluphenazine decanoate

Kane 1983 compared a low dose of fluphenazine decanoate (1.25 mg to 5 mg for two weeks) to the standard dose (12.5 mg to 50 mg for two weeks).

6.2 Specific antipsychotics

6.2.1 Clozapine

Tamminga 1994 used clozapine in a mean (± SD) dose of 293.8 mg ± 171.9 mg a day for 12 months.

6.2.2 Risperidone

Four studies used risperidone in a dose ranging from 1.5 mg a day to 16 mg a day (Bai 2003; Caroff 2011; Chan 2010; Chouinard 1995).

6.2.3 Olanzapine

Three studies used olanzapine in a dose ranging from 7.5 mg a day to 12.6 mg a day (Caroff 2011; Chan 2010), Bai 2005 did not report the dose.

6.2.4 Amisulpride

Bai 2005 used amisulpride but did not report the dose.

6.2.5 Quetiapine

Two studies used quetiapine in a dose ranging from 100 mg a day to 400 mg a day (Caroff 2011; Emsley 2004).

6.2.6 Ziprasidone

Caroff 2011 used ziprasidone in a flexible dose of 40 mg.

6.2.7 Haloperidol

Seven studies used haloperidol in doses ranging from 2 mg a day to 34 mg a day (Chouinard 1995; Emsley 2004; Glazer 1990a; Kazamatsuri 1972; Kazamatsuri 1973; Lublin 1991; Tamminga 1994).

6.2.8 Molindone

Glazer 1990a used molindone in a dose from 75 mg to 145 mg.

6.2.9 Thiopropazate

Kazamatsuri 1972 used thiopropazate in a dose of 10 mg a day to 80 mg a day.

6.2.10 Zuclopenthixol

Lublin 1991 used zuclopenthixol in a dose from 16.5 mg a day to 26.6 mg a day.

6.3 Other drugs

6.3.1 Tetrabenazine

Kazamatsuri 1973 used tetrabenazine in a dose of 50 mg twice a day.

7. Outcomes

7.1 General

The included studies presented outcomes in graphs, inexact P values of differences, or a statement of significant or non-significant difference. This made it impossible to acquire raw data for synthesis. We were unable to extract some continuous outcomes due to missing number of participants or missing means, standard deviations, or standard errors. All included studies used the LOCF strategy for the ITT analysis of dichotomous data.

7.2 Scales used to measure the TD symptoms

We have shown details of the scales that provided usable data below. We have provided reasons for exclusions of data under 'Outcomes' in the Characteristics of included studies tables.

7.2.1 Abnormal Involuntary Movement Scale (AIMS)

The AIMS (Guy 1970) is a 12-item scale consisting of a standardised examination followed by questions rating orofacial, extremity, and trunk movements, as well as three global measurements. Each of these 10 items can be scored from 0 (none) to 4 (severe). Two additional items assess dental status. The AIMS ranges from 0 to 40, with higher scores indicating greater severity.

7.2.2 Extrapyramidal symptom rating scale (ESRS)

The ESRS was developed to assess four types of drug-induced movement disorders (DIMD): parkinsonism, akathisia, dystonia, and TD (Chouinard 2005). The score for TD, ranging from 0 to 42, is based on the sum of all seven items in the TD objective examination.

7.2.3 St. Hans Rating Scale for extrapyramidal syndromes (SHRS)

The SHRS is a multidimensional rating scale for the evaluation of antipsychotic-induced hyperkinesia, parkinsonism, akathisia, and dystonia (Gerlach 1993). Each item is rated from 0 (not present) to 6 (present to an extreme degree). This gives a total score from 0 to 48 for hyperkinesia and parkinsonism.

7.3 Scales used to measure adverse events related to antipsychotic medication

7.3.1 Simpson-Angus Scale (SAS)

The SAS (Simpson 1970) is a 10-item scale, with a scoring system of 0 to 4 for each item, that measures drug-induced parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of parkinsonism.

7.3.2 Barnes Akathisia Scale (BAS)

The BAS (Barnes 1989) is a 12-item scale consisting of a standardised examination followed by questions rating orofacial, extremity, and trunk movements, as well as three global measurements. Each of these 10 items can be scored from 0 (none) to 4 (severe). Two additional items assess dental status. The BAS ranges from 0 to 40, with higher scores indicating greater severity.

7.3.3 UKU-Side Effect Rating Scale

The UKU was developed to provide a comprehensive side effect rating scale with well-defined and operationalised items to assess the side effects of psychopharmacological medications (Lingjaerde 1987). The scoring sheet includes 48 items with higher scores indicating more side effects.

7.4 Scales used to measure mental state and behaviour

7.4.1 Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms (Overall 1962). The original scale has 16 items, although a revised 18-item scale is commonly used. Total scores can range from 0 to 126. Each item is rated on a seven-point scale, with high scores indicating more severe symptoms.

7.4.2 Positive and Negative Syndrome Scale (PANSS)

The PANSS is a medical scale used for measuring symptom severity of people with schizophrenia (Kay 1986). The individual is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers.

7.4.3 Clinical Global Impression

The CGI is a three-item scale commonly used in studies on schizophrenia to enable clinicians to quantify severity of illness and overall clinical improvement (Guy 1976). The items are: severity of illness, global improvement, and efficacy index. A seven-point scoring system is usually employed with low scores indicating decreased severity or greater recovery, or both.

Excluded studies

There are 133 excluded studies (163 references); the majority (n = 74) were excluded because they were not randomised. Thirty-nine studies included participants with schizophrenia or other mental disorders who did not have TD. One study did not provide separate data from the included minority with TD; we contacted study authors who confirmed that these data were not available. Five studies investigated interventions that were not relevant for this review. Seven studies were cross-over studies that did not provide data from the phase before crossing over to the next treatment. We contacted authors for three of these studies: author of Lal 1974 confirmed that no separate data were available, and we received no reply from authors of Lieberman 1988 or NDSG 1986, which were also excluded as they were published over 20 years ago and we assumed it very unlikely to receive a reply with data so many years later. We did not find up-to-date contact details for authors of four of the cross-over studies (Bateman 1979; Delwaide 1979; Schwartz 1990; Singer 1971), and decided to also exclude these as they were published 25 to 45 years ago and we assumed it very unlikely to receive a reply so many years later. Seven studies did not provide any usable data. Authors of five of these studies (Herz 1991; Johnson 1987; Quinn 1984; Spohn 1988; Spohn 1993) confirmed that no further data were available. Authors of one of these studies did not reply (Andia 1998) and we could not find up-to-date contact details for authors of a final study (Borison 1987). We excluded these two studies as they were published 15 to 25 years ago and we assumed it very unlikely to receive a reply with data so many years later.

Studies awaiting classification

There are currently no studies awaiting assessment for inclusion in this review.

Ongoing studies

There is one ongoing study (N0546099389), which compares quetiapine and risperidone. This study was excluded in the previous review, but we have decided to move it to the ongoing

studies section. It is a record from a trial registry, and at the time of preparing this update we were unable to locate author contact details or any more information about the study.

Risk of bias in included studies

Please refer to Figure 2 and Figure 3 for graphical overviews of the risk of bias in the included studies.

Allocation

While all 13 included studies stated that they randomised participants, we considered only three studies to be at low risk of selection bias. Two of these studies explicitly described how they generated the randomisation sequence (Chan 2010; Kane 1983), whereas one described block randomisation with stratification, and we assumed low risk of bias (Cookson 1987). None of the studies described how they concealed allocation and we rated all of them at unclear risk of selection bias.

Blinding

Eight studies stated that they were conducted on a double-blind basis, but none tested the blindness of raters, clinicians and trial participants. Only four studies (Bai 2003; Caroff 2011; Chouinard 1995; Glazer 1990a) explicitly described how they blinded participants and personnel, and we rated them at low risk of performance bias. Five studies did not mention blinding of participants or personnel, or that the study was double-blind (Bai 2005; Chan 2010; Emsley 2004; Kazamatsuri 1973; Lublin 1991); these studies were at high risk of performance bias. The remaining four studies were at unclear risk of performance bias; they stated that the study was double-blind but did not describe further details of blinding.

Six studies had blinded raters and were at low risk of detection bias (Bai 2003; Chan 2010; Kazamatsuri 1972; Kazamatsuri 1973; Lublin 1991; Tamminga 1994). The remaining seven studies were at unclear risk of detection bias.

Incomplete outcome data

Eight studies were at low risk of attrition bias; they either had no dropouts (Cookson 1987) or low dropout rate and reported on dropouts adequately (Bai 2003; Bai 2005; Chan 2010; Chouinard 1995; Glazer 1990a; Kazamatsuri 1972; Lublin 1991). Five studies had a greater than 30% loss to follow-up (Caroff 2011; Emsley 2004; Kane 1983; Tamminga 1994), or unbalanced loss to follow-up between groups (Kazamatsuri 1973), and did not report outcomes for participants lost to follow-up. These studies were rated at high risk of attrition bias. In all cases, however, we tried to ensure that every person randomised was analysed.

Selective reporting

The majority of data in this review originates from published reports. Most of the included studies reported expected outcomes (impact on TD symptoms). Only two trials fully reported outcomes outlined in protocols and were at low risk of reporting bias (Bai 2005; Chan 2010). Four trials were at unclear risk of bias, as we have had no opportunity to see protocols of these trials to compare the outcomes reported in the full publications with what was measured during the conduct of the trial (Bai 2003; Cookson 1987; Glazer 1990a; Tamminga 1994). Seven studies did not report results of all outcomes listed in the methods section fully (Caroff 2011; Chouinard 1995; Emsley 2004; Kane 1983; Kazamatsuri 1972; Kazamatsuri 1973; Lublin 1991) and were at high risk of reporting bias. Attempts to contact authors of trials for additional data were mostly unsuccessful, but we did receive some additional data from four of the trialists (Cookson 1987; Caroff 2011; Chouinard 1995; Kane 1983).

Other potential sources of bias

Four studies reported details such as baseline characteristics with sufficient detail to rate them at low risk of other bias. Four studies were at unclear risk of other bias, three (Kazamatsuri 1973; Kazamatsuri 1972; Lublin 1991) because of insufficiently detailed reporting to rule out any other bias, and one (Tamminga 1994) because the report was on a preliminary analysis with four of 49 subjects not yet having completed the study. Despite randomisation, two studies reported having unequal groups at baseline on important prognostic factors, and thus were at high risk of other bias (Cookson 1987; Glazer 1990a). Three studies randomised participants with schizophrenia, and this review included secondary reports of post hoc analyses of participants with TD. These studies were therefore at high risk of other bias (Caroff 2011; Chouinard 1995; Kane 1983).

Effects of interventions

See: **Summary of findings for the main comparison** Reduced dose of antipsychotics compared with antipsychotic maintenance for antipsychotic-induced tardive dyskinesia; **Summary of findings 2** Antipsychotic cessation compared with antipsychotic maintenance for antipsychotic-induced tardive dyskinesia; **Summary of findings 3** Switch to another antipsychotic compared with antipsychotic cessation for antipsychotic-induced tardive dyskinesia; **Summary of findings 4** Switch to a specific antipsychotic compared with switch to a different specific antipsychotic for antipsychotic-induced tardive dyskinesia; **Summary of findings 5** Specific antipsychotic compared with other drugs for antipsychotic-induced tardive dyskinesia

* indicates primary outcomes.

Comparison 1. Reduced overall dose of antipsychotic versus antipsychotic maintenance

1.1 TD symptoms

We had chosen 'No clinically important improvement in TD symptoms' for any time period as a primary outcome, with clinically important improvement defined as more than 50% improvement on any TD scale. Although the data we found in trials did not fit this exactly we feel that the outcome 'not improved to a clinically important extent' fits best with what we had hoped to find.

The authors of two RCTs of antipsychotic reduction provided additional data (Cookson 1987; Kane 1983).

1.1.1 No clinically important improvement*

No clinically important improvement in TD severity was associated with antipsychotic reduction compared with antipsychotic maintenance at 44 to 48 weeks (very low-quality evidence, 2 RCTs, 17 people, RR 0.42 95% CI 0.17 to 1.04, Analysis 1.1).

1.1.2 Not any improvement

When the outcome criterion was broadened from clinically significant improvement to improvement of any degree in TD severity, the result persisted at 44 to 48 weeks (very low-quality evidence, 2 RCTs, 17 people, RR 0.42 95% CI 0.17 to 1.04, Analysis 1.2).

1.1.3 Deterioration of symptoms

Antipsychotic reduction was not associated with deterioration of TD symptoms compared with continued dose at 44 to 48 weeks (very low-quality evidence, 2 RCTs, 17 people, RR 0.61 95% CI 0.11 to 3.31, Analysis 1.3).

1.2 General mental state

1.2.1 Relapse

The number of those relapsing was equivocal over the long term (1 RCT, 8 people, RR 3.00 95% CI 0.16 to 57.36, Analysis 1.4).

1.3 Acceptability of the treatment: leaving the study early

The number of people leaving the study early was not statistically different for either the antipsychotic reduction group (1/4) or the antipsychotic maintained group (3/4) at 44 to 48 weeks (very low-quality evidence, 1 RCT, 8 people, RR 0.33 95% CI 0.06 to 1.99, Analysis 1.5).

We did not identify any studies that reported on adverse events, hospital and service utilisation outcomes, economic outcomes, social confidence, social inclusion, social networks, personalised quality of life, behaviour, or cognitive state.

1.4 Subgroup analysis

1.4.1 Clinical stage: recent-onset TD

It was not possible to evaluate whether those with recent-onset TD responded differently to those with more established problems, since neither trial reported data for groups with different durations of TD that could be extracted for separate analyses.

1.4.2 Duration of follow-up

We were unable to investigate any effects that a reduced dose of antipsychotics may have had in relation to duration of follow-up because both studies had very similar length: 44 and 48 weeks.

1.5 Heterogeneity

Data were homogeneous. We did not detect clinical, methodological or statistical heterogeneity as described in Assessment of heterogeneity.

1.6 Sensitivity analyses

1.6.1 Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. As both studies stated that they randomised participants, we have not undertaken this sensitivity analysis.

1.6.2 Assumptions for lost binary data

At the time of updating this review, we were unable to compare the findings with completer data only, as the previous review authors held data received from study authors.

1.6.3 Risk of bias

We judged both studies in this comparison to be at high risk of bias across one or more domains. Therefore, we were unable to perform a sensitivity analysis in this instance.

1.6.4 Imputed values

We would have undertaken a sensitivity analysis to assess the effects of including data from cluster-randomised trials where we used imputed values for ICC in calculating the design effect, however, no cluster-randomised trials were included in this comparison.

1.6.5 Fixed-effect and random-effects models

We also synthesised data for the primary outcome using a random-effects model. This did not alter the significance of the results (2 RCTs, 17 people, RR 0.43, 95% CI 0.17 to 1.08).

Comparison 2. Switch to a specific antipsychotic versus placebo (cessation of antipsychotic)

2.1 TD symptoms

2.1.1 No clinically important improvement*

One study found a benefit in favour of antipsychotics against placebo for clinically important improvement in TD symptoms at 12 weeks (low-quality evidence, 1 RCT, 42 people, RR 0.45 95% CI 0.23 to 0.89, Analysis 2.1).

2.1.2 Average difference in severity of TD at the end of the trial

TD symptoms were also measured using the continuous AIMS scale (see Description of studies, Outcomes). One study found a beneficial effect of antipsychotics when comparing average endpoint scores of the AIMS to placebo at 12 weeks (very low-quality evidence, 1 RCT, 42 people, MD -5.50 95% CI -8.60 to -2.40, Analysis 2.2).

2.2 General mental state

2.2.1 Average difference in severity of psychiatric symptoms at the end of the trial

General mental state was measured using the continuous BPRS scale (see Description of studies, Outcomes). One study found no difference between antipsychotics and placebo on average endpoint score of the BPRS at 12 weeks (1 RCT, 42 people, MD -4.30 95% CI -10.48 to 1.88, Analysis 2.3).

2.3 Acceptability of the treatment: leaving the study early

Using antipsychotics did not significantly increase the chances of a person leaving the study early at 12 weeks (very low-quality evidence, 1 RCT, 50 people, RR 0.60 95% CI 0.16 to 2.25, Analysis 2.4).

2.4 Adverse effects

2.4.1 Extrapyramidal symptoms*: need of antiparkinsonism drugs

We found no difference in the use of antiparkinsonism drugs between antipsychotic and placebo at 12 weeks (1 RCT, 48 people, RR 2.08 95% CI 0.74 to 5.86, Analysis 2.5).

2.4.2 Average change in extrapyramidal adverse effects: Parkinsonism

One study measured parkinsonism on the continuous ESRS scale (see above). No difference was found between antipsychotics and

placebo at 12 weeks (1 RCT, 42 people, MD -0.40 95% CI -1.25 to 0.45, Analysis 2.6).

2.4.3 Average change in extrapyramidal adverse effects: Dystonia

One study measured dystonia using the continuous ESRS scale. No difference was found between those allocated to antipsychotics or placebo at 12 weeks (1 RCT, 42 people, MD -0.70 95% CI -1.76 to 0.36, Analysis 2.7).

We did not identify any studies that reported on hospital and service utilisation outcomes, economic outcomes, social confidence, social inclusion, social networks, personalised quality of life, behaviour, or cognitive state.

We also did not identify any studies that investigated the effect on TD of antipsychotic cessation compared with antipsychotic maintenance.

2.5 Subgroup and sensitivity analyses

There was only one included study in this comparison, and this study did not report on subgroups. Consequently, subgroup and sensitivity analyses were not carried out.

Comparison 3. Switch to a specific antipsychotic versus switch to another specific antipsychotic

3.1 TD symptoms

3.1.1 No clinically important improvement*

None of the four studies that reported on this outcome found a clinically important difference on improvement in TD symptoms between two specific antipsychotics (Analysis 3.1): short-term: thiopropazate versus haloperidol (low-quality evidence, 1 RCT, 20 people, RR 1.53, 95% CI 0.58 to 4.05), zuclopenthixol versus haloperidol (low-quality evidence, 1 RCT, 15 people, RR 1.00, 95% CI 0.79 to 1.27); medium-term: olanzapine versus risperidone (low-quality evidence, 1 RCT, 60 people, RR 1.25, 95% CI 0.82 to 1.90), quetiapine versus haloperidol (low-quality evidence, 1 RCT, 45 people, RR 0.80, 95% CI 0.52 to 1.22); long-term: quetiapine versus haloperidol (low-quality evidence, 1 RCT, 45 people, RR 0.88, 95% CI 0.64 to 1.21).

3.1.2 Not any improvement

Neither of the two studies that reported on any improvement of TD symptoms found a difference between two specific antipsychotics (Analysis 3.2): short-term: thiopropazate versus haloperidol (low-quality evidence, 1 RCT, 20 people, RR 0.41, 95% CI 0.05 to 3.28), zuclopenthixol versus haloperidol (low-quality evidence, 1 RCT, 15 people, RR 0.88, 95% CI 0.16 to 4.68).

3.1.3 Deterioration of symptoms

Neither of the two studies that reported on deterioration of TD symptoms found a difference between two specific antipsychotics (Analysis 3.3): short-term: thiopropazate versus haloperidol (low-quality evidence, 1 RCT, 20 people, RR 1.22, 95% CI 0.09 to 16.92), zuclopenthixol versus haloperidol (low-quality evidence, 1 RCT, 15 people, RR 0.88, 95% CI 0.16 to 4.68).

3.1.2 Average difference in severity of TD at the end of the trial

A short-term (two weeks) study of people with established withdrawal-exacerbated TD found no difference on endpoint AIMS scores after the first week (1 RCT, 18 people, MD 1.87, 95% CI -0.20 to 3.94) for the groups receiving molindone or haloperidol at the standard dosage range. Results for the second week, using higher 'masking' dosages, significantly favoured the haloperidol group (1 RCT, 18 people, MD 3.44, 95% CI 1.12 to 5.76). Another short-term study comparing zuclopenthixol and haloperidol found no difference between groups on endpoint SHRS scores (1 RCT, 15 people, MD -4.81, 95% CI -12.15 to 2.53). Finally, a medium-term study found no difference between olanzapine and risperidone on endpoint AIMS scores (1 RCT, 60 people, MD 2.20, 95% CI -0.53 to 4.93). See Analysis 3.4.

3.1.4 Average change in severity of TD during the trial period

One study found amisulpride favourable to olanzapine in reducing TD symptoms measured by AIMS change from baseline scores at medium term (1 RCT, 54 people, MD 2.48, 95% CI 0.44 to 4.52). Three other comparisons found no difference between specific antipsychotics at medium term: olanzapine versus unspecified FGAs (1 RCT, 53 people, MD 1.66, 95% CI -0.45 to 3.77), amisulpride vs unspecified FGAs (1 RCT, 53 people, MD -0.82, 95% CI -2.85 to 1.21), and olanzapine vs risperidone (1 RCT, 60 people, MD 1.20, 95% CI -2.58 to 4.98, Analysis 3.5).

3.2 General mental state

3.2.1 Deterioration of mental state

No difference was found in the proportion with deterioration of mental state between specific antipsychotics: zuclopenthixol versus haloperidol at short term (1 RCT, 15 people, RR 0.30, 95% CI 0.01 to 6.29), olanzapine versus risperidone at medium term (1 RCT, 60 people, RR 1.00, 95% CI 0.15 to 6.64), quetiapine versus haloperidol at long term (1 RCT, 45 people, RR 1.83, 95% CI 0.62 to 5.39, Analysis 3.6).

3.2.2 Average difference in severity of psychiatric symptoms at the end of the trial

No difference was found in average endpoint scores of the PANSS between quetiapine and haloperidol at long term (1 RCT, 45 people, MD -2.20, 95% CI -6.02 to 1.62, Analysis 3.7).

3.2.3 Average change in severity of psychiatric symptoms during the trial period

There was also no difference on the average endpoint scores on the BPRS between specific antipsychotics at medium term: olanzapine versus unspecified FGAs (1 RCT, 53 people, MD -1.14, 95% CI -4.79 to 2.51), amisulpride versus unspecified FGAs (1 RCT, 53 people, MD -2.46, 95% CI -6.27 to 1.35), olanzapine versus risperidone (1 RCT, 60 people, MD -1.70, 95% CI -8.37 to 4.97), and olanzapine versus amisulpride (1 RCT, 54 people, MD 1.32, 95% CI -1.94 to 4.58, Analysis 3.8).

3.3 Acceptability of the treatment: leaving the study early

In the short term, a specific antipsychotic did not significantly increase the chances of a person leaving the study early compared with another specific antipsychotic: molindone versus haloperidol (1 RCT, 18 people, MD not estimable, there were no events), thiopropazate versus haloperidol (1 RCT, 20 people, MD 0.24, 95% CI 0.01 to 4.44, Analysis 3.9). In the medium term, switching to olanzapine significantly reduced the chances of a person leaving the study early compared with switching to risperidone (2 RCTs, 170 people, RR 0.73 95% CI 0.57 to 0.95, I^2 = 0, Analysis 3.10) or compared with switching to quetiapine (1 RCT, 116 people,

RR 0.70 95% CI 0.54 to 0.90). For all other comparisons between specific antipsychotics at medium term, there was no difference in the chances of a person leaving the study early: olanzapine versus unspecified FGAs (1 RCT, 56 people, RR 1.86, 95% CI 0.18 to 19.38), amisulpride versus unspecified FGAs (1 RCT, 55 people, RR 0.96, 95% CI 0.06 to 14.65), olanzapine versus amisulpride (1 RCT, 57 people, RR 1.93, 95% CI 0.19 to 20.12), olanzapine versus ziprasidone (1 RCT, 82 people, RR 0.77, 95% CI 0.56 to 1.05), quetiapine versus risperidone (1 RCT, 118 people, RR 1.05, 95% CI 0.88 to 1.25), quetiapine versus ziprasidone (1 RCT, 90 people, RR 1.10, 95% CI 0.86 to 1.40), ziprasidone versus risperidone (1 RCT, 84 people, RR 0.95, 95% CI 0.74 to 1.23). Finally, in the long term, there was no difference between clozapine and haloperidol (1 RCT, 39 people, RR 3.36, 95% CI 0.45 to 25.16), or between quetiapine and haloperidol on the number leaving the study early (1 RCT, 45 people, RR 1.31, 95% CI 0.63 to 2.69, see Analysis 3.11).

3.4 Adverse events

3.4.1 Extrapyramidal symptoms*: need of antiparkinsonism drugs

A study comparing risperidone and haloperidol found no difference between groups at medium term (1 RCT, 37 people, RR 0.68, 95% CI 0.34 to 1.35, Analysis 3.12). Another study found that participants allocated to haloperidol were more likely to need antiparkinsonism drugs than those allocated to quetiapine in the long term (1 RCT, 45 people, RR 0.45, 95% CI 0.21 to 2.96, Analysis 3.12).

3.4.2 Average change in extrapyramidal adverse effects: Parkinsonism

Symptoms of parkinsonism were measured using the continuous SAS, SHRS, and ESRS scales (see Description of studies, Outcomes). At short term, one study found no difference in parkinsonism symptoms measured by SHRS endpoint scores between zuclopenthixol and haloperidol (1 RCT, 15 people, MD -4.81, 95% CI -12.15 to 2.53, Analysis 3.13). One study found those allocated to olanzapine were less likely to develop symptoms of parkinsonism than those allocated to risperidone measured by ESRS change scores at medium term (1 RCT, 60 people, MD -0.70, 95% CI -1.33 to -0.07). For all other comparisons between specific antipsychotics at medium term, there was no difference in symptoms of parkinsonism as measured by average change scores: olanzapine versus unspecified FGAs (1 RCT, 53 people, MD -0.85, 95% CI -2.55 to 0.85), amisulpride versus unspecified FGAs (1 RCT, 53 people, MD -0.50, 95% CI -2.45 to 1.45), and olanzapine versus amisulpride (1 RCT, 54 people, MD -0.35, 95% CI -2.44 to 1.74, Analysis 3.14).

3.4.3 Average change in extrapyramidal adverse effects: Dyskinesia

Symptoms of dyskinesia were measured using the continuous ESRS scale. There was no difference in symptoms of dyskinesia between those switching to olanzapine and those switching to risperidone (1 RCT, 60 people, MD 0.30, 95% CI -0.91 to 1.51, Analysis 3.15).

3.4.4 Average change in extrapyramidal adverse effects: Akathisia

Symptoms of akathisia were measured using the continuous BAS and ESRS scales (see Description of studies, Outcomes, Analysis 3.16). There was no difference in symptoms of akathisia for those switching to olanzapine (1 RCT, 53 people, MD 0.08 95% CI -0.30 to 0.46) or amisulpride (1 RCT, 53 people, MD -0.11 95% CI -0.42 to 0.20) compared with those remaining on unspecified FGAs. There was also no difference for those switching to olanzapine compared with those switching to risperidone (1 RCT, 60 people, MD -0.80 95% CI -1.76 to 0.16) or amisulpride (1 RCT, 54 people, MD 0.19 95% CI -0.12 to 0.50).

3.4.5 Average change in extrapyramidal adverse effects: Dystonia

Symptoms of dystonia were measured using the continuous ESRS scale. There was no difference in symptoms of dystonia in those switching to olanzapine compared with those switching to risperidone (1 RCT, 60 people, MD -0.70 95% CI -1.41 to 0.01, Analysis 3.17).

3.4.6 Average change in general adverse events

General adverse events were measured using the continuous UKU scale (see Description of studies, Outcomes, Analysis 3.18). There was no difference in general adverse events for those switching to olanzapine (1 RCT, 53 people, MD 0.08 95% CI -1.85 to 2.01) or amisulpride (1 RCT, 53 people, MD -0.55 95% CI -2.33 to 1.23) compared with those remaining on unspecified FGAs. There was also no difference for those switching to olanzapine compared with those switching to amisulpride (1 RCT, 54 people, MD 0.63 95% CI -0.93 to 2.19).

3.5 Global state

3.5.1 Average change in global state

Global state was measured using the continuous CGI scale (see Description of studies, Outcomes, Analysis 3.19). There was no difference in change scores of global state in those switching to olanzapine (1 RCT, 53 people, MD -0.07 95% CI -0.41 to 0.27) or amisulpride (1 RCT, 53 people, MD -0.19 95% CI -0.47 to 0.09) compared with those remaining on FGA. There was also no difference in those switching to olanzapine compared with those switching to risperidone (1 RCT, 60 people, MD 0.10 95% CI -0.61 to 0.81) or amisulpride (1 RCT, 54 people, MD 0.12 95% CI -0.19 to 0.43).

We did not identify any studies that reported on hospital and service utilisation outcomes, economic outcomes, social confidence, social inclusion, social networks, personalised quality of life, behaviour, or cognitive state.

3.6 Subgroup and sensitivity analyses

There were no meta-analyses for the primary outcomes of this comparison because studies were stratified by antipsychotic medication. Consequently, we did not carry out subgroup and sensitivity analyses.

Comparison 4. Specific antipsychotic versus other drug

4.1 TD symptoms

4.1.1 No clinically important improvement*

One study found no difference between haloperidol and tetrabenazine for clinically important improvement in TD symptoms at 24 weeks (very low-quality evidence, 1 RCT, 13 people, RR 1.07 95% CI 0.51 to 2.23, Analysis 4.1).

4.1.2 Not any improvement

One study found no difference between haloperidol and tetrabenazine for the outcome 'no improvement in TD symptoms' at 24 weeks (1 RCT, 13 people, RR 2.57 95% CI 0.35 to 18.68, Analysis 4.2).

4.1.3 Deterioration of symptoms

One study found no difference on deterioration of TD symptoms between haloperidol and tetrabenazine at 24 weeks (very low-quality evidence, 1 RCT, 13 people, RR 0.86 95% CI 0.07 to 10.96, Analysis 4.3).

4.2 Acceptability of the treatment: leaving the study early

One study found no difference in the proportion of people leaving the study early between haloperidol and tetrabenazine at 24 weeks (very low quality-evidence, 1 RCT, 13 people, RR 4.38 95% CI 0.25 to 76.54, Analysis 4.4).

We did not identify any studies that reported on mental state, adverse events, hospital and service utilisation outcomes, economic outcomes, social confidence, social inclusion, social networks, personalised quality of life, behaviour, or cognitive state.

4.3 Subgroup and sensitivity analyses

There was only one included study in this comparison, and this study did not report on subgroups. Consequently, we did not carry out subgroup and sensitivity analyses.

DISCUSSION

Summary of main results

1. The search

This area of research does not seem to be active. We have identified additional data, but most trials predate the year 2000; only three were carried out after, published in 2004 to 2011. This could be due to a decreased concern with TD, or less emergence of the problem in research-active communities because of more thoughtful use of antipsychotic drugs or loss of faith in potential treatments.

2. Few data

Only a little over 700 people were included in this review. It is possible that real and important effects have not been highlighted because of the necessarily wide CIs of the findings. Many outcomes were not measured at all by the included studies (see Overall completeness and applicability of evidence), including one of our outcome measures that was selected as important. We may have been overambitious in hoping for some of these outcomes in TD trials, but simple reporting of social impact and quality of life is of particular interest to patients and carers. Finally, we did not identify any RCTs of participants with TD that compared antipsychotic cessation with antipsychotic maintenance.

3. Outcomes

3.1 Tardive dyskinesia symptoms

We found low-quality evidence of clinically important improvement in TD symptoms for switching antipsychotic to risperidone compared with antipsychotic cessation (with placebo) after 12 weeks (RR 0.45, 95% CI 0.23 to 0.89, 1 study, 42 participants). Because the quality of the evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

For the remaining comparisons: antipsychotic reduction versus maintenance, switch to a new antipsychotic versus switch to a different new antipsychotic, and specific antipsychotic versus other drug, we found low to very low-quality evidence of little or no difference between groups for no clinically important improvement in TD symptoms and deterioration of TD symptoms, but again, our confidence in these results is limited due to the poor-quality evidence, not least because there were few participants (13 to 60 participants per comparison).

3.2 Adverse effects

There was low-quality evidence of fewer people that needed antiparkinsonism medication due to extrapyramidal side effects after switching to quetiapine compared with haloperidol after one year (RR 0.45, 95% CI 0.21 to 0.96, 1 study, 45 participants). Due to the low quality of this evidence, our confidence in these results is limited. For the other comparisons, switch to haloperidol or risperidone versus antipsychotic cessation, and risperidone versus haloperidol, we found very low-quality evidence of little or no difference between groups. Therefore, we are very uncertain about these results, not least because there were few participants (37 and 48 participants per comparison).

3.3 Mental state

We found low- to very low-quality evidence of little or no difference in mental state: relapse, deterioration of mental state, or average endpoint scores on scales measuring mental state, between groups of the following comparisons: antipsychotic reduction versus maintenance, switch to risperidone versus antipsychotic cessation, switch to zuclopenthixol versus haloperidol, switch to olanzapine versus risperidone, and switch to quetiapine versus haloperidol. Again, our confidence in these results is limited due to the poor quality of evidence, not least because there were few participants (8 to 60 participants per comparison).

3.4 Acceptability of treatment: leaving the study early

It is always unclear what leaving a study early means. It could be related to the participant not accepting treatment for a series of reasons, or to participants finding the trial intolerable. It also could be a function of a trial design in which willing participants are still asked to leave because of some degree of protocol violation.

There was very low-quality evidence for most of the comparisons that the number of participants leaving the study early was no different in either group. The small number of people randomised in these comparisons (8 to 170 participants) made the likelihood of an unequivocal outcome unlikely. However, we found very low-quality evidence that fewer participants allocated to olanzapine left the study early compared with risperidone and compared with quetiapine. Since evidence was of very low quality for both comparisons, we have very little confidence in the effect estimates and CIs; the true effects are likely to be substantially different.

3.5 Social confidence, social inclusion, social networks, or personalised quality of life

We selected this group of outcomes for the 2017 review update following a service-user consultation, as being of importance to patients. We did not identify any studies that reported on any of these outcomes.

Overall completeness and applicability of evidence

1. Completeness

No outcomes in this review involved large numbers of people. There is a large literature of trials assessing the impact of antipsychotic reduction or cessation, or both, on outcomes such as symptoms and relapse. Much of the initial impetus for these trials was derived from concerns about antipsychotic-induced TD. It was disappointing to note that many of these trials did not systematically assess TD, and thus were not suitable for inclusion in this review. While many trials of antipsychotic reduction and/or cessation assess TD, the baseline and endpoint means are rarely presented for those with TD at baseline. Two authors (Cookson 1987; Kane 1983) kindly provided raw data from which we could extract the impact of antipsychotic reduction on those with TD at baseline. The very small sample size limits the confidence that one can place on the equivocal results.

Post hoc analyses of the main efficacy and safety analyses for the newer atypicals have also been undertaken (for example, Caroff 2011 and Chouinard 1995). The analyses of results from these trials need to be interpreted with caution for several reasons: (a) suboptimal design for the assessment of treatment of TD (for example, pre-entry washout or gradual conversion to study drug); (b) the analyses were post hoc; and (c) differences in results between different arms in the studies may reflect antipsychotic suppression due to differing dosing strategies.

There were no data on the patient-designated important outcomes social confidence, social inclusion, social networks, or personalised quality of life, nor were there data on hospital and service utilisation outcomes, economic outcomes, behaviour or cognitive response.

2. Applicability

Trial participants were mostly men in their 50s with schizophrenia in hospital, but were nevertheless people who would be recognisable in everyday care.

Reducing or stopping antipsychotic medication may not be clinically prudent in some situations. The current lack of evidence showing any improvement in TD with such strategies means that clinicians may be less inclined to use them in mentally stable patients. On the other hand, high-quality evidence in this area would be very useful and applicable in everyday clinical practice to aid in the decision making around the risk and benefits of reducing or stopping antipsychotic medication following the emergence of TD.

Quality of the evidence

Overall, the quality of the evidence is low to very low. This means that we have limited to very little confidence in the effect estimates, and the true effect may be, or is likely to be, substantially different from the estimate of the effect. The main reasons for our low confidence in the evidence were:

1. poor study methodology and reporting of methods resulting in downgrading evidence for risk of bias;
2. very small sample sizes resulting in downgrading evidence for imprecision;
3. wide CIs (often due to low event rates) that included appreciable benefit or harm for the intervention as well as no effect, resulting in downgrading evidence for imprecision.

Please see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5 for full details.

Potential biases in the review process

1. Missing studies

Every effort was made to identify relevant trials. However, these studies were all small and it is likely that we have failed to identify other studies of limited power. We do not, however, think it likely that we have failed to identify large relevant studies.

2. Missing data

We excluded 14 studies published between 1971 and 1998 that did not provide any usable data, see Excluded studies. We contacted study authors and six replied to confirm no usable data were available. Authors of three studies did not reply, and we could not find up-to-date contact details for authors of five studies (all over 25 years old). We find it very unlikely that we would receive a reply from study authors regarding research conducted so many years ago; therefore, we also excluded these studies.

3. Introducing bias

We have tried to be balanced in our appraisal of the evidence but could have inadvertently introduced bias. We welcome comments or criticisms. New methods and innovations now make it possible to report data where, in the past, we could not report data at all or had to report data in a different way. We believe the 'Summary of findings' tables are a valuable innovation – but problematic to those not ‘blind’ to the outcome data. It is possible to ‘cherry pick’ significant findings for presentation in this table. We have tried to decrease the chance of doing this by asking a new reviewer (HB) to select outcomes relevant for this table before becoming familiar with the data.

Agreements and disagreements with other studies or reviews

While the reduction or cessation, or both, of antipsychotics appears a rational first line of treatment for TD, the evidence from systematic reviews such as Gilbert 1995 highlights the very high risk of relapse associated with both antipsychotic cessation and antipsychotic reduction. In addition, there is evidence from the literature that intermittent therapy may be associated with more unfavourable TD outcomes (higher scores, fewer eventual remissions etc.) (Bergin 1992; Jeste 1979; NDSG 1986).

It is of interest to note that naturalistic studies suggest that TD fluctuates over time, and often improves in spite of continuing antipsychotic exposure (Casey 1986). Kane 1986 analysed data on 98 people followed up for at least seven years and reported that those on lower doses of antipsychotics were more likely to have an improvement in their TD. Gardos 1988 reported that improvement in TD was associated with lower antipsychotic doses after TD onset. Using a sophisticated epidemiological approach, Morgenstern 1993 looked at risk factors for new cases of TD. Higher average antipsychotic medication was associated with an increased risk of developing persistent TD. However, Cavallaro 1993

assessed TD prognosis (persistent, remitting etc) with respect to antipsychotic dose change (decreased, increased, unchanged) in 125 inpatients followed up for three years. They found no significant association between antipsychotic reduction and improved TD outcome. As with all uncontrolled studies, these data need to be interpreted cautiously, because those who have less responsive psychoses may require higher doses and have higher rates of TD regardless of treatment.

Also of note, in more recent years commentators are more likely to concede that no change in antipsychotic medications may be required for those with TD (Gardos 1994). Casey 1986 suggested, "therefore, antipsychotics in low to moderate doses are not contra-indicated in patients with psychosis and will not inevitably aggravate TD" (p. 89). There is some evidence to suggest that younger people (under 60 years) who develop TD are three times more likely to recover when compared with those who develop TD after that age (Smith 1980). One interpretation of the data would suggest that, for younger people who develop TD that is not associated with significant impairment, no change to treatment is required other than regular monitoring and reassurance.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with tardive dyskinesia

Currently, this review has no data derived from randomised controlled trials (RCTs) that can adequately support the notion that any particular antipsychotic is an effective treatment for tardive dyskinesia (TD). While products such as clozapine, and the newer 'atypical' antipsychotics such as risperidone have favourable extrapyramidal adverse effect profiles compared with classical antipsychotics, it remains to be seen if these products are associated with lower incidence rates of TD.

2. For clinicians

This review cannot provide clinicians with an effective treatment algorithm involving antipsychotic medications for the treatment of people with TD. While many practice guidelines continue to recommend antipsychotic reduction or cessation, or both (APA 1992; Barnes 1993; Jeste 1993; Shale 1996), this treatment option lacks a sound evidence-base. There are a considerable amount of RCT-derived data that demonstrate that this intervention is not safe because of the increased risk of relapse of psychoses (Gilbert 1995).

As outlined in the Background section of this review, there are features related to the interactions between antipsychotics and TD that need to be taken into account when assessing the evidence presented in this review. In particular, TD is thought to worsen in the short term following antipsychotic dose reduction and/or cessation, and TD is thought to be suppressed or masked in the short term following antipsychotic dose increment. These factors combine to favour antipsychotics when compared with placebo for the treatment of TD.

3. For managers and policy makers

There are no adequate data available from this review to provide evidence for managers and policy makers on best practice.

Implications for research

1. General

The power of this review would have been greatly enhanced by better reporting of data. For example, only three studies made explicit how randomisation was undertaken, and none described allocation concealment. We realise that much of the work for these trials predates CONSORT, which was first published in 1996 (Begg 1996), and that it is only too easy to judge studies of the past by standards of today. Future studies, however, should report to a much higher standard.

2. Specific

2.1 Reviews suggested by excluded studies

As is usual with systematic reviews, we had to exclude several studies that contained comparisons that were in some way related to movement disorders and their treatment. In the case of this review, every one of these trials should have an existing Cochrane Review in which to be considered (Table 2).

2.2 Trials

There is a need to assess the utility of second-generation antipsychotics in the management of established TD. The recent literature highlights the finding that TD can be found in people with schizophrenia who have never been treated, thus challenging basic assumptions about the causality of TD (Waddington 1988). Research is required to differentiate underlying vulnerability to movement disorders (that may be part of a latent trait underlying schizophrenia and TD) from that proportion of TD causally related to antipsychotic use. Research is required that can separate out the variable trajectory inherent in young and midlife-onset TD from the impact of traditional and 'atypical' antipsychotics.

Well-designed RCTs, involving a large number of participants over protracted periods of time, are needed if we are to see what role antipsychotics could have in prevention and treatment of TD. Such studies are of importance to people with the problem (Figure 1) and have long been ignored.

2.2.1 Use of cross-over design

Trialists find it difficult to identify people with both TD and schizophrenia to participate in trials (Schmidt 1991). Randomised, cross-over design is used in the hope of improving the power of the study to find outcomes of interest. This design initially asks participants to be randomised to one of the experimental interventions, and then, at a pre-specified time, to be crossed over to the treatment that they did not at first receive. Conditions with a more stable time course than TD are better suited for cross-over studies (Fleiss 1984). Further difficulties are related to the carry-over effect. Unless cross-over studies include a mid-study washout period (where the person is free of treatment before starting the next arm of the study), any effect of the first intervention may continue into the second half placebo arm of the trial – the 'carry-over effect'. Also, carry-over may involve the re-growth or retreat of neuroreceptors. This slow re-balancing, if started, could continue long after all traces of intervention drugs are gone, so physiological half-life of the experimental treatment may not be the only variable to consider when thinking though the issues of carry-over. TD is also an unstable condition and people with TD may not remain compliant with medication. All these factors make the arguments

for not using cross-over methodology strong, despite the initial attraction (Armitage 1991; Fleiss 1984; Pocock 1983).

2.2.2 Length of study

Only five studies included in this review (Caroff 2011; Cookson 1987; Emsley 2004; Kane 1983; Tamminga 1994) used the intervention for more than six months. TD, however, is a chronic condition of insidious onset, the severity of which fluctuates spontaneously (APA 1992). Another problem in TD research is that spontaneous, age-related, non-neuroleptic-induced dyskinesias occur in people with schizophrenia (Fenton 2000). The spontaneous dyskinetic movements are more prevalent in older age and appear identical to the movements of antipsychotic-induced tardive dyskinesia (Fenton 2000). In addition, since reducing or switching antipsychotic may have a swift but reversible effect (Cavallaro 1993; Smith 1980), it is the long-term outcomes that must be considered of most clinical value.

2.2.3 Outcomes

Scale-derived data do have their place. Trials most commonly used the AIMS scale. This is a very widely applied tool utilised to measure the severity of symptoms of those who have TD. The use of this scale to measure change as a result of treatment is, however, problematic (Bergen 1984). It is therefore important that a scale is validated for measuring changes secondary to treatment in those with TD. In addition, many of the outcomes we initially desired when we started this review have not been investigated. Finally, a service user consultation also informed the addition of outcomes of special importance to patients. We have reconsidered all these outcomes in case they were too ambitious and tried to tailor them to a real-world pragmatic trial design (see Table 3).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bai 2003

Methods	Allocation: "randomly assigned", not described Blindness: "double blind", partially described Design: parallel groups Setting: inpatients, Taiwan Duration: 12 weeks
Participants	Diagnosis: schizophrenia with persistent severe TD (DSM IV, Kane criteria) N = 49 randomised, 42 completed Age: 50.2 (SD 9.7) years Sex: 28 men and 14 female History: maintenance on conventional antipsychotics for > 1 year with an equivalent dosage of < 200 mg/d of chlorpromazine; duration of TD not reported
Interventions	After a 4-week washout period with all original conventional antipsychotics discontinued: 1. Risperidone: started at 2 mg/d and increased, with a 2-mg increase every 2 weeks, to 6 mg/d over 6 weeks; then maintenance dose 6 mg/d for 12 weeks. N = 22 2. Placebo: placebo for 12 weeks. N = 20 Concomitant medication included benzodiazepines (86%-90%) and antiparkinsonism drugs (50%-86%)
Outcomes	TD symptoms: AIMS Adverse effects: extrapyramidal symptoms (parkinsonism) (ESRS) Adverse effects: dystonia (ESRS) TD symptoms: clinical efficacy (decrease in AIMS of 3 or 4 = responder) BPRS
Notes	Sponsorship source: supported by Janssen-Cilag Taiwan, Johnson & Johnson Taiwan Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects were randomly assigned to the risperidone or placebo groups", further details not reported

Bai 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" "A placebo with an identical appearance to the risperidone dose was prescribed for the placebo group using the same dose schedule."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The TD condition was evaluated blindly by a psychiatrist with the Abnormal Involuntary Movement Scale (AIMS) every 2 weeks"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Forty-two patients completed the 12-week study and 7 subjects withdrew. Four subjects dropped out due to psychotic symptom exacerbation (2 subjects during the washout period: 1 subject in the placebo group and 1 subject in the risperidone group). Another 3 subjects withdrew due to a medical condition (infectious disease, heart condition, and lung carcinoma)."
Selective reporting (reporting bias)	Unclear risk	Unclear if all pre-defined outcomes were reported. A protocol is not available for verification.
Other bias	Low risk	The study seems to be free of other sources of bias.

Bai 2005

Methods	Allocation: "randomized", not described Blindness: "single blind", partially described Design: parallel groups Setting: Inpatients, Taiwan Duration: 24 weeks
Participants	Diagnosis: schizophrenia (DSM IV), Schooler and Kane's criteria for persistent TD N = 80 Age: 50.2 (SD 7.1) years Sex: 39 men and 41 women History: duration of TD not reported; treatment with conventional antipsychotics for > one year
Interventions	No washout period on the discontinuation of all conventional antipsychotics was reported 1. Olanzapine: dose not reported, 24 weeks. N = 27 2. Amisulpride: dose not reported, 24 weeks. N = 27 3. First generation antipsychotic (FGA): dose not reported, 24 weeks. N = 26
Outcomes	TD symptoms: AIMS Adverse effects: extrapyramidal side effects (SAS) Adverse effects: akathisia (BAS) Adverse effects: general (UKU) General mental state (BPRS) Leaving the study early

Bai 2005 *(Continued)*

Notes	Sponsorship source: the study was supported by grants from National Science Council, Taiwan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects were randomized to three groups", further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"single-blind and controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"single-blind and controlled study" Blinding details of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Finally 76 cases (95%) completed the 24-week study, 2 cases in the olanzapine groups withdrew due to impaired liver function, 1 case in the amisulpride group due to infectious disease, and 1 case in the FGA controlled groups withdrew due to unstable psychiatric condition" “All data were analyzed on an intent-to-treat basis, and endpoint data were generated with the last observation carried forward (LOCF).”
Selective reporting (reporting bias)	Low risk	All outcomes appear to have been reported
Other bias	Low risk	The study seems to have been free of other sources of bias.

Caroff 2011

Methods	Allocation: "randomly assigned", not described Blindness: "double blind", partially described. Design: post hoc analysis of parallel-group RCT Setting: inpatients, USA Duration: 18 months
Participants	Diagnosis: schizophrenia and TD (DSM IV, Schooler-Kane criteria) N = 200 Age: 47.2 (SD 9.4) years (18-65 years) Sex: 158 men and 42 women History: duration of TD not reported
Interventions	Overlap in administration of the antipsychotic drugs that participants received before study entry was permitted for the first 4 weeks after randomisation to allow a gradual transition to study medication: 1. Oolanzapine: flexible dose of 7.5 mg each day/twice a day/3 times a day/4 times a day for 18 months. N = 54

Caroff 2011 *(Continued)*

	2. quetiapine: flexible dose of 200 mg each day/twice a day/3 times a day/4 times a day for 18 months. N = 62 3. Rrisperidone: flexible dose of 1.5 mg each day/twice a day/3 times a day/4 times a day for 18 months. N = 56 4. ziprasidone: flexible dose of 40 mg each day/twice a day/3 times a day/4 times a day for 18 months. N = 28 Medications were flexibly dosed with 1-4 capsules daily, as judged by the study doctor. Concomitant medications were permitted, except for additional antipsychotic agents.
Outcomes	Leaving the study early Unable to use - AIMS, PANSS, SAS, BAS, cogitive composite score (not reported in means and SDs for the separate intervention groups)*
Notes	Sponsorship source: supported by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, National Institute of Mental Health. This article was based on results from the CATIE project, supported by the National Institute of Mental Health. Astra Zeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Forest Pharmaceuticals, Inc., Janssen Pharmaceutica Products, L.P., Eli Lilly and Company, Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Zenith Goldline Pharmaceuticals, Inc., provided medications for the studies. This material is based upon work also supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research Development, with resources and the use of facilities at the Philadelphia Veterans Affairs Medical Center. *Study author kindly replied to our request for data. At the time of preparing this review no more outcome data were available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were initially randomly assigned", further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...double-blind conditions..." "Identical-appearing capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), perphenazine (8 mg), or ziprasidone (40 mg)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	The primary clinical outcome measure was time to all-cause treatment discontinuation. Total population (N = 200): 74% discontinuation olanzapine: 31/54 (57%); quetiapine: 51/62 (82%); risperidone: 44/56 (79%); zipraidone: 21/28 (75%). Reasons for withdrawal reported
Selective reporting (reporting bias)	High risk	Original CATIE study: "The primary clinical outcome measure was time to all-cause treatment discontinuation. Secondary outcomes included discontinuations for intolerability, inefficacy, and patient decision; rates of discontinuations; mean modal dose; and change from baseline in the PANSS and neurocognitive composite scores/".TD: "The primary outcome measure used to evaluate the course of TD was change from baseline in total AIMS score. Secondary outcome measures included change in global, distress, and impair-

Caroff 2011 *(Continued)*

		ment of function items on the AIMS; percentage of patients meeting Schooler-Kane criteria for at least 2 consecutive visits post baseline; percentage of visits at which patients met modified Schooler-Kane criteria; and percentage of patients with at least a 50% change in AIMS score (excluding month 1). In addition, treatment differences with respect to all cause discontinuation are described for patients with TD at baseline."
Other bias	High risk	Post hoc analysis; modified diagnostic criteria for TD were applied at baseline, and a 3-month history of antipsychotics exposure was not required.

Chan 2010

Methods	Allocation: "randomly assigned by coin method" Blindness: single-blind (outcome assessor) Design: parallel groups Setting: inpatients, Taiwan Duration: 24 weeks
Participants	Diagnosis: schizophrenia (58) and schizoaffective disorder (2) (DSM-IV criteria); antipsychotic-induced TD N = 60 Age: 45.3 (SD 11.6) years (range 18-70 years) Sex: 21 men and 39 women History: duration of TD not reported. Antipsychotic exposure ˜10 years. All of the participants received FGAs prior to participation in this study.
Interventions	Following a washout period of 3-7 days: 1. risperidone: flexible dose of 1.9 ± 0.7 (baseline) to 4.1 ± 1.4 (end point) mg/d for 24 weeks. N = 30 2. olanzapine: flexible dose of 8.1 ± 2.0 (baseline) to 12.6 ± 5.4 (end point) mg/d for 24 weeks. N = 30
Outcomes	TD symptoms: no clinical improvement > 50% (AIMS) TD symptoms: AIMS Adverse effect: dyskinesia Adverse effect: parkinsonism Adverse effect: dystonia Adverse effect: akathisia Adverse effects: general adverse events (39/30 vs 31/30) General mental state: BPRS Leaving the study early
Notes	Sponsorship source: supported by research grant from the Taoyuan Mental Hospital and from the Department of Health, Executive Yuan, Taiwan

Risk of bias

Bias	Authors' judgement	Support for judgement

Chan 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	"randomly assigned to receive either olanzapine or risperidone with a 1-to-1 ratio by coin method with a 6-block design".
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"...primary care physicians and patients were not blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“Two investigators (C.-H.C. and J.-J.C.) served as blinded raters.” "The BPRS, CGI-S, AIMS and global impression of ESRS were performed at baseline and at weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 or at end point visit by blinded-rater"
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/30 in the risperidone and 7/30 in the olanzapine groups dropped out from the study; reasons reported. "All patients who were randomly assigned and had at least 1 post-baseline assessment were included in the intent-to-treat (ITT) analysis. If the ITT subjects withdrew from the study earlier than scheduled, then the last observation carried forward method was employed to extend the end point scores."
Selective reporting (reporting bias)	Low risk	Data for all outcomes in the trial registry, NCT00621998, have been reported.
Other bias	Low risk	The study seems to be free of other sources of bias.

Chouinard 1995

Methods	Allocation: "randomly assigned", not described Blindness: "double blind", partially described Design: post hoc analysis of parallel, 6-group RCT Setting: inpatients, Canada Duration: 8 weeks
Participants	Diagnosis: chronic schizophrenia (DSM-III R criteria) N = 135 Age: mean 39 years, range 19-60 years Sex: 34 men and 14 women History: duration TD not reported; the most common pre-study medications were haloperidol, procyclidine, lorazepam, benztropine and chlorpromazine; the most commonly used depot antipsychotic agents were haloperidol decanoate, fluphenazine decanoate, flupenthixol decanoate and pipothiazine palmitate.
Interventions	Mean duration of washout phase 6 days. 1. Risperidone: dose 2 mg/d for 8 weeks. N = 8 2. Risperidone: dose 6 mg/d for 8 weeks. N = 6 3. Risperidone: dose 10 mg/d for 8 weeks. N = 6 4. Risperidone: dose 16 mg/d for 8 weeks. N = 11

Chouinard 1995 *(Continued)*

	5. Haloperidol: dose 20 mg/d. N = 6 6. Placebo: N = 11 "At the time of selection, all psychotropic and antiparkinsonism medications were discontinued"; "no other psychotropic medication was administered except for chloral hydrate or a benzodiazepine if a sedative/hypnotic was required.", "An antiparkinsonian medication (biperiden or procyclidine) was given in case of the emergence of clinically significant drug-induced parkinsonism and dystonia"
Outcomes	Adverse events: use of antiparkinsonism medication Unable to use (data does not have variability measures, and only reports differences from baseline to worst scores) - ESRS: dyskinesia symptoms total score, CGI severity dyskinesia, buccolinguomasticatory factor, choreoathetoid factor
Notes	Sponsorship source: not reported. Study author kindly replied to our request for data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of raters not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	33% of participants terminated the study early due to insufficient therapeutic response. All early terminations were included in the ITT analysis
Selective reporting (reporting bias)	High risk	Outcomes not fully reported
Other bias	High risk	Subgroup with TD

Cookson 1987

Methods	Allocation: "allocated randomly", not described Blindness: "double blind", not described Design: parallel groups Setting: inpatients, UK Duration: 44 weeks

Cookson 1987 *(Continued)*

Participants	Diagnosis: hebephrenic or paranoid schizophrenia (ICD-9 and Feighner criteria) N = 18 (only 9 people had TD at baseline) Age: mean 44.5 years Sex: 12 men and 6 women History: duration of TD not reported; patients resistant to low doses of antipsychotics but improved with higher dosages and maintained this improvement for at least 3 months
Interventions	No washout period before study entry 1. Antipsychotic reduction: dose 50% previous dose of cis(z)-flupenthixol decanoate, bi-weekly. N = 5 2. Antipsychotic maintenance: dose standard dosage of cis(z)-flupenthixol decanoate. N = 4 Procyclidine allowed during study. Supplementary antipsychotics allowed were haloperidol (oral) or zuclopenthixol decanoate (depot). Amitriptyline used for depression
Outcomes	TD (AIMS derived) Unable to use - Adverse effects: GSES (no usable data) General mental state: BPRS (no usable data)
Notes	Dr Cookson kindly provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized in blocks of 4 and stratified by antipsychotic dose and gender", implies adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No allocation concealment details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants seem to have completed the study
Selective reporting (reporting bias)	Unclear risk	All outcomes proposed in the methods were reported, but some were not presented adequately. No protocol available to check
Other bias	High risk	"The randomised allocation of the small number of patients in the pilot study results in inequalities between the 2 groups at entry and confounded comparisons of group mean values during the study"

Emsley 2004

Methods	Allocation: "randomly assigned", not described

Emsley 2004 *(Continued)*

	Blindness: investigators blinded Design: parallel group Setting: inpatients and outpatients, South Africa Duration: 50 weeks
Participants	Diagnosis: schizophrenia (DSM IV), TD (Schooler and Kane criteria) N = 45 Age: 49.2 (SD 14.5) years, range 18-65 years Sex: 16 men and 29 women History: duration of TD not reported; at least 3 months' antipsychotic exposure; patients with established psychiatric disorder who did not receive clozapine
Interventions	After an initial screening visit, subjects were tapered from all psychotropic medication over a 2-week period. 1. Quetiapine: dose 100 mg/d increased to 400 mg/d. N = 22 2. Haloperidol: dose 5 mg/d increased to 10 mg/d. N = 23 Concomitant medications allowed were benzodiazepines for agitation or insomnia and anticholinergic agents in the event of treatment-emergent or worsening EPS. Medications not allowed were other antipsychotics or other medication known to improve or exacerbate movement disorders.
Outcomes	TD symptoms: no clinical improvement Leaving the study early General mental health PANSS Unable to use - Adverse effects: ESRS, EPS (no usable data) Global assessment: CGI. (data in graphs, no variability)
Notes	Sponsorship source: supported in part by the Medical Research Council of South Africa, Cape Town, and the University of Stellenbosch. Trial medication and monitoring of the study were provided by AstraZeneca, Wilmington, Del.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were then randomly assigned", further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"investigator-blinded", further blinding details not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"investigator-blinded", further blinding details not reported
Incomplete outcome data (attrition bias)	High risk	43% dropouts (including the 2 participants excluded in the early stages). 10/22 (45%) quetiapine and 8/23 (35%) haloperidol participants dropped out.

Emsley 2004 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Adverse effects: extrapyramidal symptoms (other than dyskinesia) not fully reported
Other bias	Low risk	The study seems to be free of other sources of bias. Baseline characteristics were balanced in the compared groups.

Glazer 1990a

Methods	Allocation: "randomly assigned", not described Blindness: double, "identical capsules" Design: parallel groups Setting: outpatients, USA Duration: 2 weeks
Participants	Diagnosis: schizophrenia or schizoaffective disorder with TD (operational criteria) and criterion for withdrawal-exacerbated TD N = 18 Age: mean 47 years Sex: 55% women History: duration of TD at least 3 months; "Patients had been receiving at least a year of continuous treatment with antipsychotics other than molindone or haloperidol"; "After a week on one of these two medications at pre-established doses equivalent to that of the pre-study neuroleptic"
Interventions	Antipsychotic medications were tapered over a 7-10 d period and then withdrawn, with single-blind substitution of placebo for 7-14 d. Study medication was administered when there was a demonstrable increase in involuntary movements. 1. Molindone: dose 75 mg (mean) during the first week (100% of pre-trial dose equivalent) and 145 mg (mean) (200% of pre-trial dose equivalent) during the second week. N = 9 2. Haloperidol: dose 19.3 mg (mean) (100% of pre-trial dose equivalent) during the first week and 34.3 mg (mean) (200% of pre-trial dose equivalent) during the second week. N = 9 Concomitant medications: psychoactive medications including antiparkinsonism agents, within 6 months before study entry were not allowed
Outcomes	Clinical improvement: AIMS Leaving the study early Unable to use - Mental state: BPRS Websters Parkinson Rating Scale: no usable data
Notes	Sponsorship source: supported in part by a grant from E.I. DuPont Pharmaceutical Company and National Institute of Mental Health Grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned to receive either molindone or haloperidol in a double-blind fashion", further details not reported

Glazer 1990a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" "Medication was supplied in identical-appearing red capsules containing 25 mg and 5 mg, respectively, of molindone and haloperidol"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind". Details of blinding of outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants completed the trial
Selective reporting (reporting bias)	Unclear risk	Unclear if psychiatric symptoms, dyskinetic movements and parkinsonism measured by BPRS and Webster Parkinsonism Rating Scale were defined as outcomes. Only AIMS results were reported.
Other bias	High risk	The two groups were comparable except for a greater past hospitalisation duration in the molindone as compared with haloperidol-treated group

Kane 1983

Methods	Allocation: randomised using random numbers table Blindness: double Design: parallel groups Setting: outpatients, USA Duration: 48 weeks
Participants	Diagnosis: schizophrenia or schizoaffective disorder (RDC) N = 8 Age: range 17-60 years Sex: not reported History: in a state of remission or at a stable clinical plateau
Interventions	1. Fluphenazine decanoate: low dose 1.25 mg-5 mg/2 weeks. N = 4 2. Fluphenazine decanoate: antipsychotic maintenance: standard dose 12.5 mg-50 mg/2 weeks. N = 4 Procyclidine, 5 mg-20 mg/d, was allowed if needed to treat extrapyramidal side effects. No other psychotropic medication except flurazepam or diazepam was allowed (these benzodiazepines were used sparingly for insomnia).
Outcomes	TD ('no clinical improvement'; 'no improvement'; 'deterioration'), reported as adverse effects Incidence of TD (modified versions of SDS) Leaving the study early General mental state: relapse Unable to use - GAS, BPRS, CGI, SAS
Notes	Sponsorship source: this investigation was supported in part by grants from the National Institute of Mental Health.

Kane 1983 *(Continued)*

	Dr Woerner kindly provided unpublished data for one site of the main study and only these are used in this review; the sex ratios are not available. If people in this study developed TD, participation was stopped and they were classified as leaving the study early.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using random numbers table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind". Details not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind". Details not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	4/8 participants left the study early
Selective reporting (reporting bias)	High risk	Not all data were reported
Other bias	High risk	Only subsample with TD from one site included in this review

Kazamatsuri 1972

Methods	Allocation: randomised Blindness: raters blind Design: parallel groups Setting: inpatients, USA Duration: 4 weeks
Participants	Diagnosis: chronic schizophrenia (15), chronic brain syndrome (3), and mental retardation (2) all manifesting typical buccolingual-masticatory oral dyskinesia due to prolonged antipsychotic medication. N = 20 Age: average 56.9 years; range 44-70 years Sex: 11 men and 9 women History: duration of TD not reported; "Before beginning this study, all patients had received tetrabenazine (56 to 156 mg daily) for six weeks "
Interventions	4-week washout using placebo medication, then: 1. haloperidol: dose 2 mg/d, increased to maximum of 16 mg/d. N = 11 2. thiopropazate: dose 10 mg/d, increased to maximum of 80 mg/d. N = 9

Kazamatsuri 1972 *(Continued)*

	Concomitant medication not reported
Outcomes	TD symptoms Leaving the study early Unable to use - Ward behaviour NOSIE (no SD)
Notes	Sponsorship source: supported in part by Public Health Service Research grant from the National Institute of Mental Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"20 patients were randomly divided", further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants not reported. Ward nurses were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Quantitative evaluation of oral dyskinesia... was carried out every two weeks, by a psychiatrist... using a blind basis". Ward nurses were also blind to the treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants dropped out from haloperidol with reasons reported.
Selective reporting (reporting bias)	High risk	Adverse effects (except for 2 participants who were discontinued from the study) were not reported. Also, oral dyskinesia and reversible EPS scores reported only as mean for each arm.
Other bias	Unclear risk	Insufficient information to make a judgement

Kazamatsuri 1973

Methods	Allocation: "randomly" Blindness: rater blind Duration: 24 weeks (4-week antipsychotic and antiparkinsonism drug cessation and placebo administration, 18-week intervention and then 2 weeks placebo) Design: parallel Setting: inpatients, USA
Participants	Diagnosis: chronic psychotic patients: chronic schizophrenia (10), mentally deficient (2), chronic brain syndrome (1); all manifesting typical buccolinguomasticatory oral dyskinesia associated with long-term antipsychotic medication N = 13 Sex: 5 women and 8 men Age: mean 55.8 years, range 41-63 years

Kazamatsuri 1973 *(Continued)*

	History: duration of TD not reported
Interventions	4 week washout from antiparkinsonism and antipsychotic medication (all replaced by placebo), then:. 1. haloperidol: dose 4 mg twice/d. From week 15 dose was doubled to 16 mg/d. N = 7 2. tetrabenazine: dose 50 mg twice/d. From week 15 onwards, dose was doubled to 200 mg/d. N = 6 Concomitant medications: "Other medications, such as antidiabetic or anticonvulsant drugs, were continued unchanged."
Outcomes	TD symptoms: not clinically improved TD symptoms: no improvement TD symptoms: deterioration Leaving the study early Unable to use - TD scale scores and adverse effects: EPS Ward behaviour (NOSIE) (means, SDs not reported)
Notes	Sponsorship source: supported in part by Public Health Service grant from the National institute of Mental Health. Tetrabenazine and placebo tablets were provided by Hoffman-La Roche.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The 13 patients were divided randomly into two groups." further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A frequency count of mouth movements (18), done by a psychiatrist blind to the study design was used to assess oral dyskinesia."
Incomplete outcome data (attrition bias) All outcomes	High risk	2/7 (29%) participants dropped out from the haloperidol group; no further details are provided for addressing the outcomes of these participants. No participants dropped out from the tetrabenazine group.
Selective reporting (reporting bias)	High risk	TD scale scores and extrapyramidal symptoms scale scores not fully reported
Other bias	Unclear risk	Insufficient information to make a judgement

Lublin 1991

Methods	Allocation: "randomised", no details

Lublin 1991 *(Continued)*

	Blindness: rater blind Design: cross-over Setting: inpatients, Denmark and Finland Duration: 18 weeks (3 weeks treatment, followed by 6 weeks washout, then crossed to another 3 weeks treatment followed by 6 weeks washout)
Participants	Diagnosis: psychotic patients with TD N = 20 Sex: 12 women and 3 men Age: mean 64.5, range 47-79 years History: duration of TD on average 5.1 years (range 0.5-11 years); duration of antipsychotic treatment on average 18.8 years (range 5-34 years)
Interventions	Participants were down-titrated to the lowest possible dose of haloperidol and kept stable for 4 weeks in order to keep them in an optimal mental condition, then: 1. haloperidol: dose 5.4 mg/d-6.2 mg/d for 3 weeks (followed by 6 weeks washout and 3 weeks zuclopenthixol). N = 15 (7 during first period and 8 during second period) 2. zuclopenthixol: dose of 16.5 mg/d-zuclopenthixol 26.6 mg/d for 3 weeks (followed by 6 weeks washout and 3 weeks haloperidol). N = 15 (8 during first period and 7 during second period) Concomitant medication: no antiparkinsonism medication was given. 4 participants (2 from each group) received benzodiazepines without changes during the study. "Other neuroleptic drugs, antidepressants and antiparkinsonian medication were not allowed"
Outcomes	TD symptoms: improvement 50% TD symptoms: not any improvement TD symptoms: deterioration Sct. Hans Rating Scale for Extrapyramidal Side Effects: parkinsonism and TD symptoms (data extracted from figure using digitisation software) Unable to use - Leaving the study early (not reported for the phase before crossing over) Adverse events: UKU (not reported) Mental state: BPRS (not reported)
Notes	Sponsorship source: sponsorship source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were then randomized to receive either HAL or ZPT", further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not reported

Lublin 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"blind evaluation of TD and parkinsonism by means of video recordings."; "All the videotapes were later randomly sequenced and blindly scored by two of the same three raters"
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 participants entered the study, 4 dropped out during randomised phases with reasons provided
Selective reporting (reporting bias)	High risk	Side effects and mental state were measured (UKU, BPRS) but not fully reported
Other bias	Unclear risk	Insufficient information to judge

Tamminga 1994

Methods	Allocation: randomised Blindness: double Design: parallel groups Setting: not reported, USA Duration: 12 months
Participants	Diagnosis: schizophrenia; diagnosis of TD of a moderate or severe degree N = 32* Age: mean 35.57 (SD 7.60) years Sex: 20 men and 12 women History: duration of TD not reported; "Before beginning the protocol, each participant was treated with a clinically optimal dose of haloperidol for an initial 1- to 6-month stabilization period"
Interventions	After the stabilisation period, each participant was withdrawn from antipsychotic treatment for 4 weeks to allow an antipsychotic-free assessment of their dyskinetic symptoms, then: 1. clozapine plus placebo: mean dose at 293.8 ± 171.9 mg/d for 12 months. N = 25 2. haloperidol plus benztropine: mean dose at 28.5 ± 23.8 mg/d for 12 months. N = 14
Outcomes	Leaving the study early Unable to use - TD symptoms (reported means only in graph)
Notes	Sponsorship source: sponsorship source not reported We contacted study authors for updated data but at the time of preparing this review no more information had been received *49 were recruited for this study but only 32 completed the blind protocol. The study authors reported only on these 32 participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were then blindly randomised to two different drug groups," further details not reported

Tamminga 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Staff, patients, and all raters were blind to the drug group; one non rating physician and one nurse were non blind to dispense medication and monitor safety"; no further details were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Staff, patients, and all raters were blind to the drug group; one non rating physician and one nurse were non blind to dispense medication and monitor safety"; no further details were provided
Incomplete outcome data (attrition bias) All outcomes	High risk	"Forty-three patients have entered the 15-month blinded study, and 4 have not yet finished. Seven participants have been withdrawn from the protocol (6 taking clozapine; one taking haloperidol). One subject from each treatment group was dropped for leukopenia.The other 5 clozapine subjects were dropped for noncompliance (1 patient), decompensation (1 patient), seizure (1 patient), hypotension (1 patient), and ECG changes (1 patient)." Data were reported for completers only.
Selective reporting (reporting bias)	Unclear risk	Unclear if all predefined outcomes were reported. Efficacy data reported in graphs as means only. A study protocol is needed for firm conclusions.
Other bias	Unclear risk	Preliminary results as 4 subjects had not completed the study.

DSM: Diagnostic and Statistical Manual of Mental Disorders
EPS: Extrapyramidal symptoms
FGA: first-generation antipsychotic
ICD-9 - International Classification of Diseases 9th edition
ITT: intention-to-treat
RDC - Research Diagnostic Criteria
TD: tardive dyskinesia
Rating Scales:
Global impression
CGI - Clinical Global Impression
Mental state
BPRS - Brief Psychiatric Rating Scale
Adverse events
AIMS - Abnormal Involuntary Movement Scale

EPS - Extrapyramidal Symptoms Scale
ESRS - Extrapyramidal side effect rating scale

GSES - General Side Effects Scale
NOSIE - Nurses Observational Scale of Inpatients Evaluation
SAS - Simpson Angus Scale
SDS - Simpson Dyskinesia Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albus 1985	Allocation: not randomised
Ananth 1977	Allocation: not randomised

Study	Reason for exclusion
Andersson 1988	Allocation: not randomised
Andia 1998	Allocation: randomised Participants: schizophrenia (DSM-III-R), N = 26, 14 with TD Intervention: haloperidol vs clozapine Outcomes: no data available for AIMS in clozapine group, the study also reported on plasma homovanillic acid levels, an outcome not relevant for this review We contacted the study authors but no information was received. This study is over 15years old and was excluded.
Asnis 1979	Allocation: not randomised
Auberger 1985	Allocation: not randomised
Barnes 2002	Allocation: random not mentioned in this short trial registration Participants: elderly patients, many started treatment with antipsychotics at start of study (no baseline TD)
Bateman 1979	Allocation: random Participants: psychiatric patients with TD Interventions: metoclopramide (10 mg, 20 mg or 40 mg) vs haloperidol (5 mg or 10 mg) Outcomes: no outcome data was provided for the first period before cross-over. We were unable to find contact details for the study authors; study is over 35 years old and was excluded
Bitter 2000	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: olanzapine vs clozapine
Blaha 1980	Allocation: not randomised
Borison 1987	Allocation: randomised Participants: schizophrenia (DSM-III criteria); TD (Schooler and Kane criteria) Interventions: molindone versus haloperidol Outcomes: no usable efficacy data; only P values were reported. We were unable to find contact details for the study authors; study is over 25 years old and was excluded
Branchey 1981	Allocation: not randomised
Brecher 1999	Allocation: randomised Participants: people with dementia, not schizophrenia, not TD at baseline
Buchanan 1992	Allocation: not randomised
Burner 1989	Allocation: 'randomly assigned' Participants: people with schizophrenia, no TD symptoms at baseline Interventions: progabide vs placebo
Buruma 1982	Allocation: randomised, cross-over Participants: "patients with tardive dyskinesia" - no further details Interventions: tiapride vs placebo

Study	Reason for exclusion
	Outcomes: doppler ratings, none before cross-over
Cai 1988	Allocation: randomisation not mentioned Participants: patients with antipsychotic-induced TD Intervention: 1-stepholidine (herbal product that has shown antipsychotic properties in animals) versus placebo Assessed and data extracted by Sai Zhao
Caine 1979	Allocation: "allocated by toss of a coin" Participants: Gilles de la Tourette's, Huntington's disease and drug-induced atypical dyskinesia, no TD symptoms at baseline Interventions: clozapine vs placebo
Calne 1974	Allocation: not randomised
Campbell 1988	Allocation: not randomised
Carpenter 1980	Allocation: not randomised
Casey 1977	Allocation: not randomised
Casey 1979	Allocation: not randomised
Casey 1981	Allocation: not randomised
Casey 1983	Allocation: not randomised
Cassady 1992	Allocation: not randomised
Chouinard 1978	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: fluphenazine ethanoate vs pipothiazine palmitate
Chouinard 1979	Allocation: random Participants: people with schizophrenia, and parkinsonism, no TD symptoms at baseline Interventions: ethopropazine vs benztropine
Chouinard 1989	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: haloperidol decanoate vs fluphenazine decanoate
Chouinard 1994	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: clozapine vs risperidone
Claveria 1975	Allocation: not randomised
Cookson 1991	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: haloperidol decanoate vs fluphenazine decanoate

Study	Reason for exclusion
Cortese 2008	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: quetiapine vs continuation of usual antipsychotic
Cowen 1997	Allocation: not randomised
Crane 1968	Allocation: not randomised, review article
Crane 1969	Allocation: not randomised
Crane 1970	Allocation: random Participants: people with schizophrenia, only 2%-3% with TD at baseline Interventions: trifluoperazine high dose vs trifluoperazine low dose vs placebo
Curran 1973	Allocation: not randomised
Curson 1985	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: fluphenazine decanoate vs placebo
Davidson 2000	Allocation: not randomised
de Jesus Mari 2004	Allocation: randomised Participants: diagnosis of schizophrenia or related disorders (DSM-IV criteria). < 50% of participants had TD at baseline Interventions: olanzapine vs "conventional antipsychotic drugs" Outcomes: author contacted for data regarding people with TD - data no longer available
Delwaide 1979	Allocation: randomised Participants: hospitalised patients with TD on a psychogeriatric ward Intervention: thioproperazine vs tiapride vs placebo Outcome: all data unusable, unable to extract data from first arm of cross-over The study is over 35 years old and we were unable to identify contact details for the author
Diamond 1986	Allocation: not randomised
Dixon 1993	Allocation: not randomised
Fahn 1983	Allocation: not randomised
Fahn 1985	Allocation: not randomised
Freeman 1980	Allocation: not randomised
Gardos 1984	Allocation: not randomised
Gerlach 1975	Allocation: random Participants: schizophrenia, no established, stable TD diagnosis at baseline Interventions: clozapine vs haloperidol

Study	Reason for exclusion
Gerlach 1978	Allocation: the randomisation was just in one arm of the study “Haloperidol + biperiden for 4 weeks (phase 2 and phase 3 in randomized sequence)”. All other arms thioridazine for 3 months, haloperidol for 4 weeks; thioridazine for 4 weeks, clozapine for 4 weeks were not Participants: elderly people with psychiatric history and neuroleptic-induced TD Interventions: biperiden vs no treatment as an adjunct to haloperidol
Gerlach 1984a	Allocation: not randomised, cohort study
Gerlach 1984b	Allocation: not randomised
Gibson 1980	Allocation: not randomised
Glazer 1984	Allocation: not randomised
Glazer 1989	Allocation: not randomised
Goldberg 1981	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: withdrawal of fluphenazine decanoate vs continuation
Greil 1984	Allocation: "randomly assigned" Participants: people with schizophrenia Interventions: biperiden vs placebo
Haggstrom 1980	Allocation: not randomised
Heresco-Levy 1993	Allocation: not randomised
Hershon 1972	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: trifluoperazine withdrawal vs trifluoperazine continuation
Herz 1991	Allocation: randomised Participants: people with schizophrenia Interventions: neuroleptic reduction (intermittent treatment) vs maintenance neuroleptic Outcomes: no usable data Dr Herz kindly replied to our request for more information. Unfortunately, individual baseline and endpoint AIMS score are no longer available
Hogarty 1976	Allocation: not randomised
Hogarty 1988	Allocation: quasi-randomised
Inada 2003	Allocation: not randomised
Inderbitzin 1994	Allocation: Not randomised ("by alternate allocation")
Jean-Noel 1999	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: clozapine vs olanzapine
Jeste 1977	Allocation: not randomised

Study	Reason for exclusion
	Participants: chronic schizophrenia with TD, N = 2 Interventions: chlorpromazine schedule A vs chlorpromazine schedule B. Treatments in the 2 groups were the same except for timing of the doses (frequency and withdrawal)
Jeste 1979	Allocation: not randomised
Johnson 1983	Allocation: not randomised
Johnson 1987	Allocation: randomised Participants: people with schizophrenia Interventions: neuroleptic dose reduction vs maintenance dose (both arms used flupenthixol decanoate) Outcomes: no usable data Dr Johnson kindly replied to our letter. No further data available from the first author
Jolley 1990	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: brief intermittent antipsychotic treatment vs fluphenazine decanoate
Jus 1979	Allocation: not randomised
Kalachnik 1984	Allocation: not randomised, case-control study Dr Kalachnick kindly provided additional information. After randomisation clinicians reviewed group allocations and re-assigned selected individuals on clinical grounds
Kane 1993	Allocation: not randomised, 2 case series
Kinon 2004	Allocation: randomised Participants: schizophrenia and TD (Schooler and Kane criteria) Interventions: olanzapine (5 mg-20 mg/d) with 1 set of intermittent dose-reduction periods versus olanzapine (5 mg-20 mg/d) with a different set of intermittent dose reduction periods
Kirch 1983	Allocation: not randomised
Kopala 2004	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: haloperidol vs risperidone
Lal 1974	Allocation: randomised, cross-over. Participants: people with schizophrenia. Interventions: thiopropazine vs trifluoperazine vs placebo. Outcomes: no usable data. Dr Lal kindly replied to inquiry. Unable to extract data from the first segment. Jadad score = 4/5
Leblanc 1994	Allocation: not randomised, cohort study
Leblhuber 1987	Allocation: not randomised
Levine 1980	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: fluphenazine withdrawal vs continuation
Lieberman 1988	Allocation: randomised

Study	Reason for exclusion
	Participants: TD according to the criteria of Schooler and Kane, schizophrenia, schizoaffective disorder, major affective disorder and attention deficit disorder Intervention: physostigmine vs bromocriptine vs benztropine vs haloperidol for 1 day, then crossed over. Outcomes: no outcome data provided for the first period before cross-over. We contacted the study author but no information received. Study is over 25 years old years old and was excluded
Lieberman 1989	Allocation: not randomised, cohort study
Lin 2006	Allocation: not randomised: naturalistic observational study
Littrell 1993	Allocation: not randomised
MacKay 1980	Allocation: "patients were divided into pairs" Participants: people with schizophrenia Intervention: lithium vs placebo
Marder 1987	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: low vs conventional-dose maintenance therapy with fluphenazine decanoate
McCreadie 1980	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: intermittent pimozide vs fluphenazine decanoate
Meco 1989	Allocation: not randomised
Miller 1994	Allocation: not randomised
NDSG 1986	Allocation: randomised cross-over Participants: psychiatric inpatients with TD Intervention: chlorprothixene vs haloperidol vs perphenazine vs haloperidol + biperiden Outcomes: no outcome data provided for the first period before cross-over We contacted the study author but no reply. Study is 30 years old and was excluded.
Newcomer 1992	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: haloperidol dose reduction vs maintained dose
Newton 1989	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: haloperidol with 'drug holiday' versus haloperidol
Odejide 1982	Allocation: randomisation not mentioned Participants: people with schizophrenia (no history of TD) Interventions: fluphenazine decanoate vs vitamin B complex
Pai 2001	Allocation: not randomised Participants: people with schizophrenia and TD Interventions: risperidone vs placebo

Study	Reason for exclusion
Paulson 1975	Allocation: not randomised Dr Paulsen kindly provided additional information about this double-blind study
Peacock 1996	Allocation: not randomised
Peluso 2012	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: FGA vs second generation antipsychotic
Perry 1985	Allocation: randomised Participants: children with autism without history of TD Dr Campbell kindly provided all published and in-press data. The authors found no difference in TD between the intermittent and continuous treatment groups but further details required for this review were not available
Pyke 1981	Allocation: not randomised
Quinn 1984	Allocation: randomised, double-blind, cross-over study Participants: people with schizophrenia Intervention: sulpiride (Dogmatil) 300 mg- 1200 mg/d Outcomes: no usable data. Drs Marsden and Quinn kindly replied to our letter, but no data suitable for this review could be provided
Quitkin 1977	Allocation: not randomised
Rapoport 1997	Allocation: not described
Ringwald 1978	Allocation: not random
Rosenheck 2003	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: haloperidol vs olanzapine
Roxburgh 1970	Allocation: not randomised
Schultz 1995	Allocation: not randomised
Schwartz 1990	Allocation: randomised Participants: psychiatric inpatients with TD Interventions: sulpiride vs placebo Outcomes: no outcome data provided for the first period before cross-over. We were unable to find contact details for the study authors; this study is over 25 years old and was excluded
Seeman 1981	Allocation: not randomised
Simpson 1978	Allocation: not randomised, cohort study
Singer 1971	Allocation: randomised Participants: psychiatric inpatients with persistent TD Interventions: thiopropazate vs placebo

Study	Reason for exclusion
	Outcomes: no outcome data provided for the first period before cross-over. We were unable to find contact details for the study authors; this study is 45 years old and was excluded
Singh 1990	Allocation: randomised Participants: people with schizophrenia (majority did not have TD) Intervention: abrupt antipsychotic withdrawal versus continuation of antipsychotic medication
Small 1987	Allocation: not randomised, cohort study
Smith 1979	Allocation: not randomised, cohort study
Soni 1984	Allocation: not randomised
Speller 1997	Allocation: randomised Participants: schizophrenia (DSM-III-R), majority with TD Intervention: amisulpride versus haloperidol Outcomes: schizophrenia symptom changes, especially negative symptoms, adverse events, and TD as adverse event. We excluded this reference because, although the majority had TD at baseline and the intervention drugs qualified, the drugs were not examined as a treatment for TD (as our inclusion criteria demand), but for negative symptoms of schizophrenia
Spivak 1997	Allocation: not randomised, cohort study
Spohn 1988	Allocation: randomised Participants: people with schizophrenia Interventions: abrupt neuroleptic cessation versus neuroleptic maintenance Outcomes: no usable data Dr Spohn kindly replied to our request for further information. Data on baseline and endpoint TD not available
Spohn 1993	Allocation: randomised Participants: people with schizophrenia Interventions: abrupt neuroleptic withdrawal versus maintenance Outcomes: no usable data Dr Spohn kindly replied to our letter, but no further data were available
Suh 2004	Allocation: randomised Participants: dementia and not TD
Thapa 1994	Allocation: randomised Participants: nursing home staff Interventions: education about neuroleptic prescribing vs no specific additional education
Tollefson 1997	Allocation: random Participants: no TD at baseline, investigates incidence of TD with long-term treatment with olanzapine vs haloperidol
Tran 1997	Allocation: random Participants: people with schizophrenia, no TD symptoms at baseline Interventions: olanzapine versus haloperidol

Study	Reason for exclusion
Turek 1972	Allocation: not randomised - allocated to treatment group in a "nonsystematic" fashion, but then participants were re-allocated to alternate groups based on clinical judgement
Williamson 1995	Allocation: random Participants: schizophrenia, not TD Interventions: olanzapine 1 mg vs olanzapine 10 mg versus placebo
Wirshing 1999	Allocation: random Participants: people with treatment-resistant schizophrenia, no TD symptoms at baseline Interventions: haloperidol vs risperidone
Wistedt 1983	Allocation: randomised Participants: people with schizophrenia (no history of TD) Interventions: fluphenazine/flupenthixol decanoate continuation vs withdrawal
Wolf 1991	Allocation: not randomised, cohort study
Wright 1998	Allocation: not randomised
Zander 1981	Allocation: not randomised
Zarebinski 1990	Allocation: not randomised, cohort study
Zeng 1994	Allocation: randomised Participants: patients with antipsychotic-induced TD Intervention: flunarizine (calcium channel antagonist) vs placebo Assessed and data extracted by Sai Zhao

FGA: first-generation antipsychotic
IV = intravenous
TD: tardive dyskinesia

Characteristics of ongoing studies *[ordered by study ID]*

N0546099389

Trial name or title	A six month, rater blind comparison of quetiapine and risperidone in the treatment of tardive dyskinesia in patients with schizophrenia
Methods	Allocation: randomised Blindness: rater blind Design: not reported Setting: not reported Duration: 6 months
Participants	People with schizophrenia with TD
Interventions	1. Quetiapine

N0546099389 *(Continued)*	2. Risperidone
Outcomes	Prevalence and severity of abnormal involuntary movements
Starting date	
Contact information	
Notes	Very limited information from two trials registries. We were unable to locate author contact details.

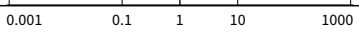
DATA AND ANALYSES

Comparison 1. Reduced overall dose of antipsychotic vs antipsychotic maintenance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: no clinically important improvement (long term)	2	17	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.04]
2 Tardive dyskinesia: no improvement (long term)	2	17	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.04]
3 Tardive dyskinesia: deterioration (long term)	2	17	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.11, 3.31]
4 General mental state: relapse (long term)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.16, 57.36]
5 Acceptability of the treatment: leaving the study early (long term)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.06, 1.99]

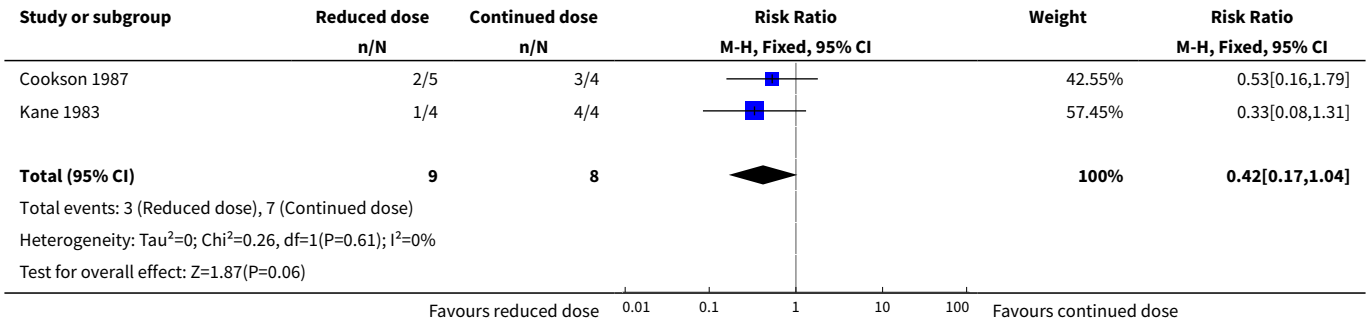
Analysis 1.1. Comparison 1 Reduced overall dose of antipsychotic vs antipsychotic maintenance, Outcome 1 Tardive dyskinesia: no clinically important improvement (long term).

Study or subgroup	Reduced dose n/N	Continued dose n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cookson 1987	2/5	3/4		42.55%	0.53[0.16,1.79]
Kane 1983	1/4	4/4		57.45%	0.33[0.08,1.31]
Total (95% CI)	**9**	**8**		**100%**	**0.42[0.17,1.04]**
Total events: 3 (Reduced dose), 7 (Continued dose)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=1(P=0.61); I^2=0%					
Test for overall effect: Z=1.87(P=0.06)					

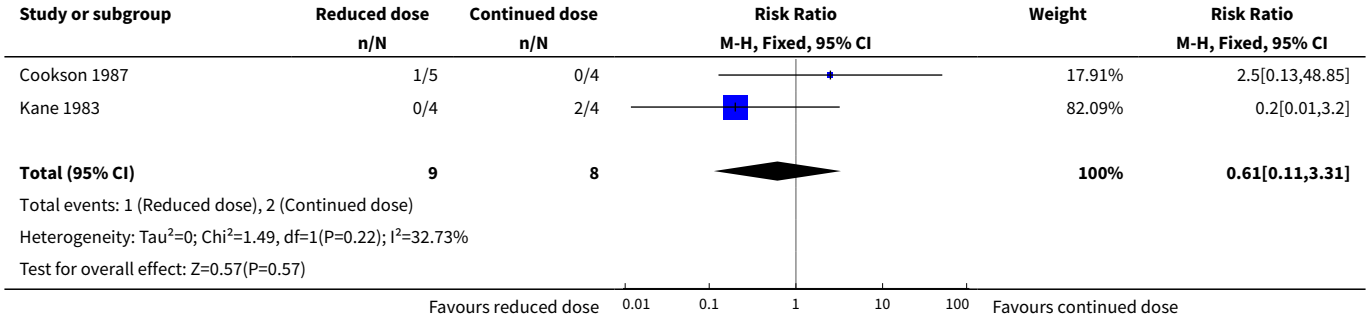


Favours reduced dose — Favours continued dose

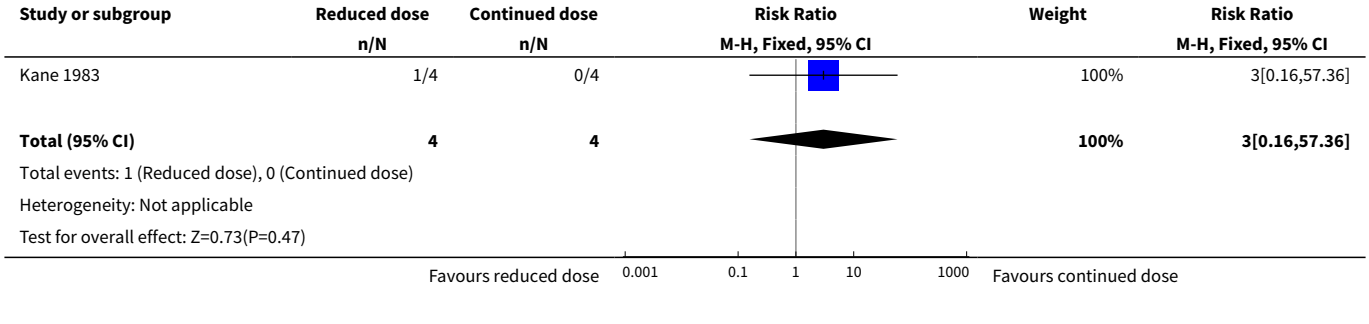
Analysis 1.2. Comparison 1 Reduced overall dose of antipsychotic vs antipsychotic maintenance, Outcome 2 Tardive dyskinesia: no improvement (long term).



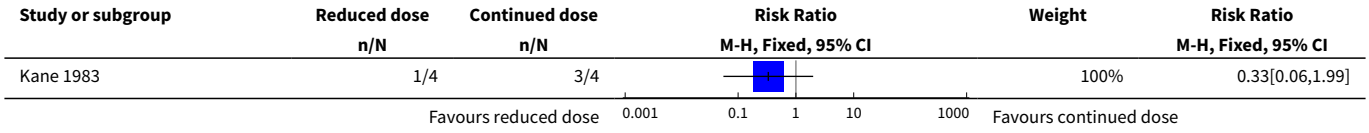
Analysis 1.3. Comparison 1 Reduced overall dose of antipsychotic vs antipsychotic maintenance, Outcome 3 Tardive dyskinesia: deterioration (long term).

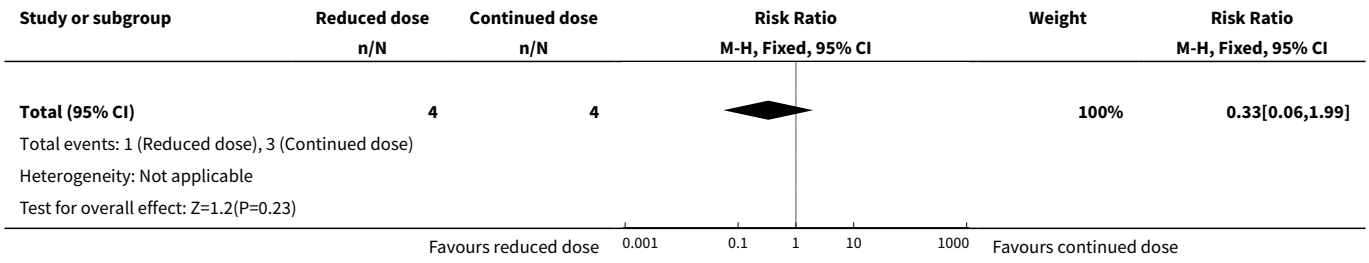


Analysis 1.4. Comparison 1 Reduced overall dose of antipsychotic vs antipsychotic maintenance, Outcome 4 General mental state: relapse (long term).



Analysis 1.5. Comparison 1 Reduced overall dose of antipsychotic vs antipsychotic maintenance, Outcome 5 Acceptability of the treatment: leaving the study early (long term).

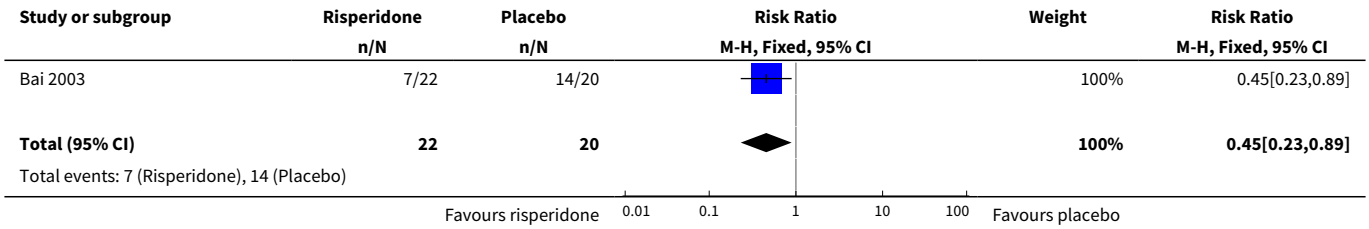


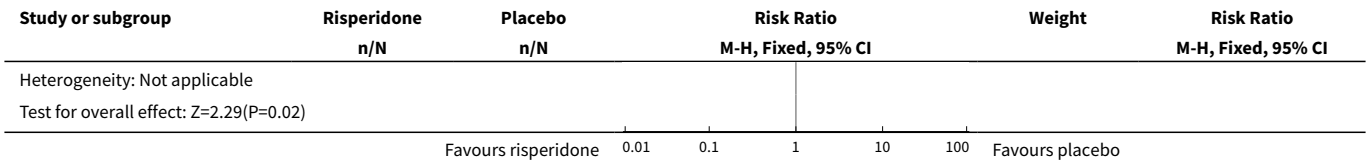


Comparison 2. Switch to specific antipsychotic vs antipsychotic cessation

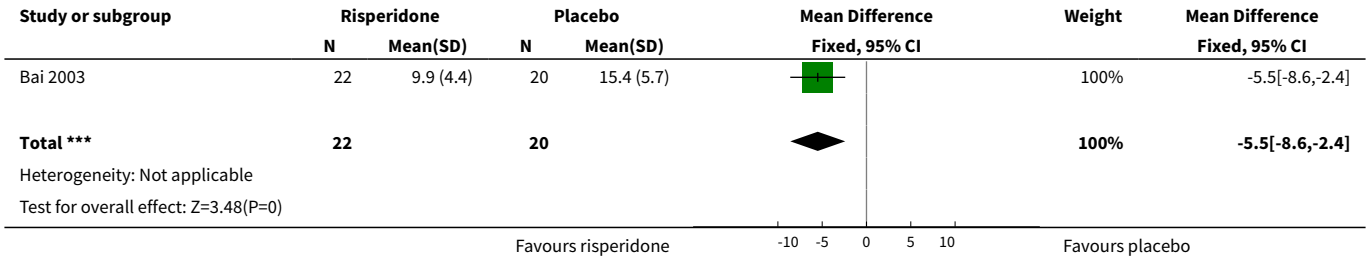
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: no clinically important improvement (medium term)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.23, 0.89]
2 Tardive dyskinesia: average endpoint score (AIMS, high = poor) (medium term)	1	42	Mean Difference (IV, Fixed, 95% CI)	-5.5 [-8.60, -2.40]
3 General mental state: average endpoint score (BPRS, high = poor) (medium term)	1	42	Mean Difference (IV, Fixed, 95% CI)	-4.30 [-10.48, 1.88]
4 Acceptability of the treatment: leaving the study early (medium term)	1	50	Risk Ratio (IV, Fixed, 95% CI)	0.6 [0.16, 2.25]
5 Adverse effects: use of antiparkinsonism drugs (medium term)	1	48	Risk Ratio (IV, Fixed, 95% CI)	2.08 [0.74, 5.86]
5.1 Haloperidol	1	12	Risk Ratio (IV, Fixed, 95% CI)	2.0 [0.56, 7.09]
5.2 Risperidone	1	36	Risk Ratio (IV, Fixed, 95% CI)	2.26 [0.37, 13.60]
6 Adverse effects: parkinsonism - average endpoint score (ESRS) (medium term)	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.25, 0.45]
7 Adverse effects: dystonia - average endpoint score (ESRS) (medium term)	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.76, 0.36]

Analysis 2.1. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 1 Tardive dyskinesia: no clinically important improvement (medium term).

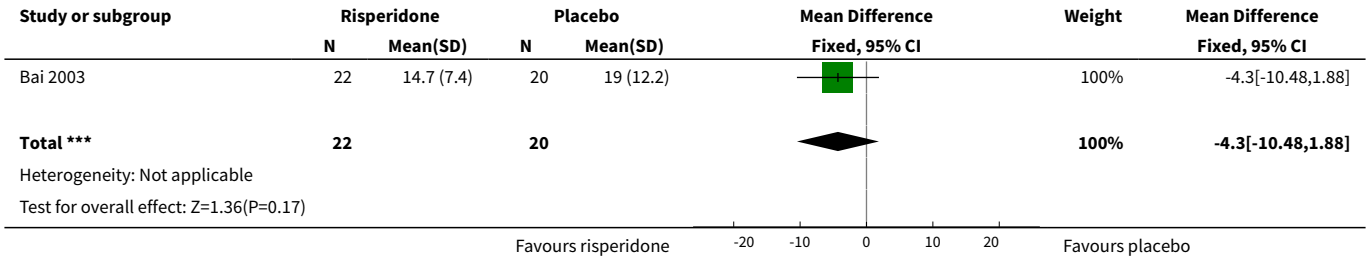




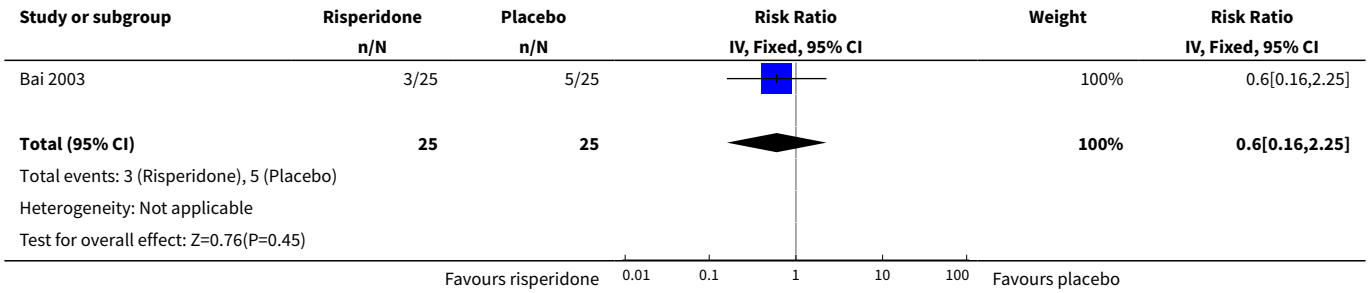
Analysis 2.2. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 2 Tardive dyskinesia: average endpoint score (AIMS, high = poor) (medium term).



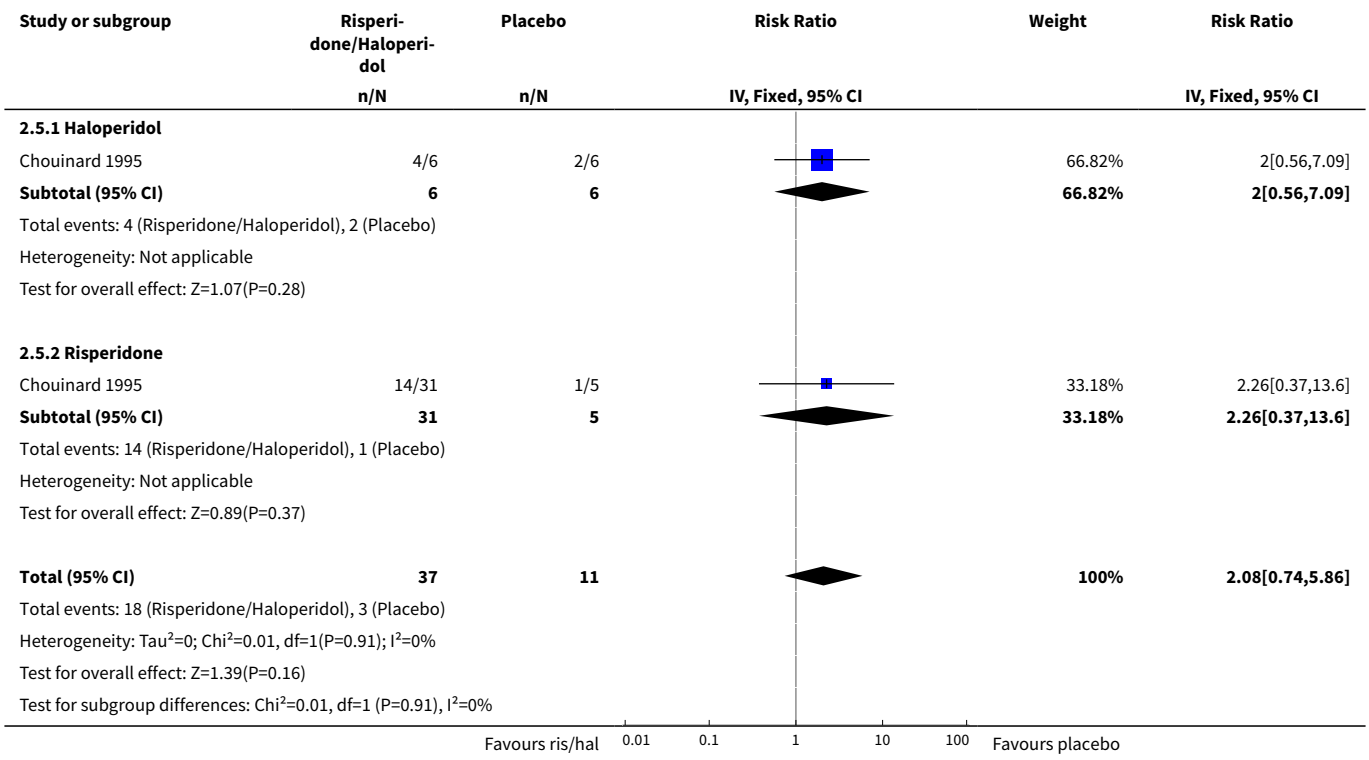
Analysis 2.3. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 3 General mental state: average endpoint score (BPRS, high = poor) (medium term).



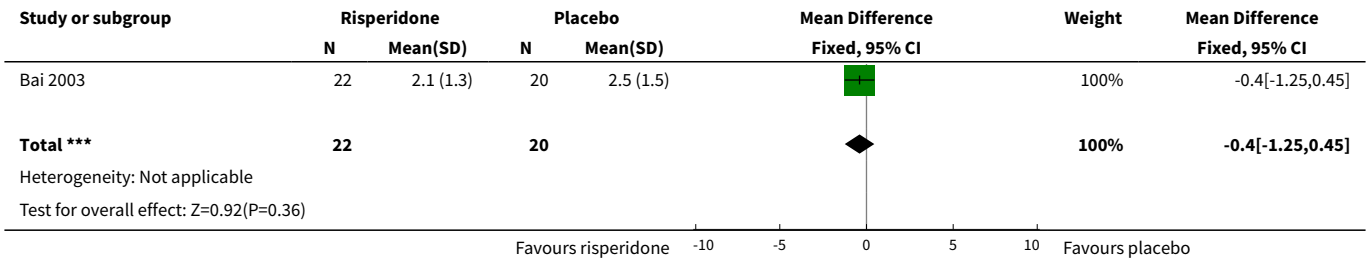
Analysis 2.4. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 4 Acceptability of the treatment: leaving the study early (medium term).



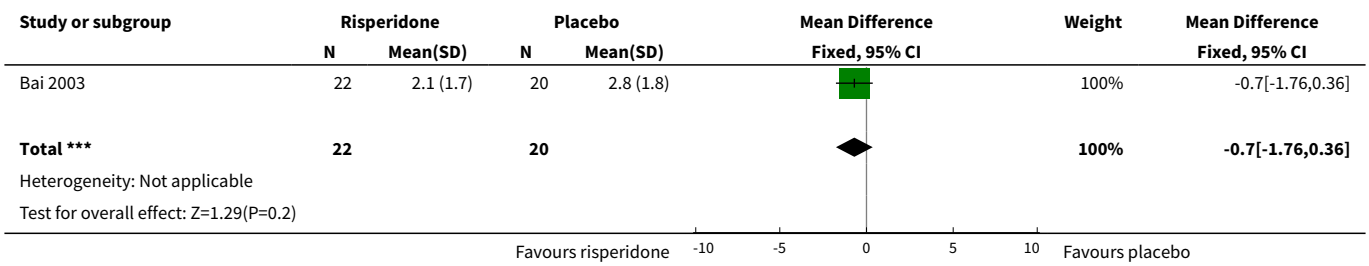
Analysis 2.5. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 5 Adverse effects: use of antiparkinsonism drugs (medium term).



Analysis 2.6. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 6 Adverse effects: parkinsonism - average endpoint score (ESRS) (medium term).



Analysis 2.7. Comparison 2 Switch to specific antipsychotic vs antipsychotic cessation, Outcome 7 Adverse effects: dystonia - average endpoint score (ESRS) (medium term).



Comparison 3. Switch to a specific antipsychotic vs switch to a different antipsychotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: no clinically important improvement	4		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1 Thiopropazate vs haloperidol - short term	1	20	Risk Ratio (IV, Fixed, 95% CI)	1.53 [0.58, 4.05]
1.2 Zuclopenthixol vs haloperidol - short term	1	15	Risk Ratio (IV, Fixed, 95% CI)	1.0 [0.79, 1.27]
1.3 Olanzapine vs risperidone - medium term	1	60	Risk Ratio (IV, Fixed, 95% CI)	1.25 [0.82, 1.90]
1.4 Quetiapine vs haloperidol - medium term	1	45	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.52, 1.22]
1.5 Quetiapine vs haloperidol - long term	1	45	Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.64, 1.21]
2 Tardive dyskinesia: not any improvement (short term)	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 Thiopropazate vs haloperidol	1	20	Risk Ratio (IV, Fixed, 95% CI)	0.41 [0.05, 3.28]
2.2 Zuclopenthixol vs haloperidol	1	15	Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.16, 4.68]
3 Tardive dyskinesia: deterioration (short term)	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
3.1 Thiopropazate vs haloperidol	1	20	Risk Ratio (IV, Fixed, 95% CI)	1.22 [0.09, 16.92]
3.2 Zuclopenthixol vs haloperidol	1	15	Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.16, 4.68]
4 Tardive dyskinesia: average endpoint score (various scales)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Molindone vs haloperidol, 100% masking dose (AIMS, short term)	1	18	Mean Difference (IV, Fixed, 95% CI)	1.87 [-0.20, 3.94]
4.2 Molindone vs haloperidol, 200% masking dose (AIMS, short term)	1	18	Mean Difference (IV, Fixed, 95% CI)	3.44 [1.12, 5.76]
4.3 Zuclopenthixol vs haloperidol (SHRS, short term)	1	15	Mean Difference (IV, Fixed, 95% CI)	-4.81 [-12.15, 2.53]
4.4 Olanzapine vs risperidone (AIMS, medium term)	1	60	Mean Difference (IV, Fixed, 95% CI)	2.20 [-0.53, 4.93]
5 Tardive dyskinesia: average change score (AIMS, low = better) (medium term)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

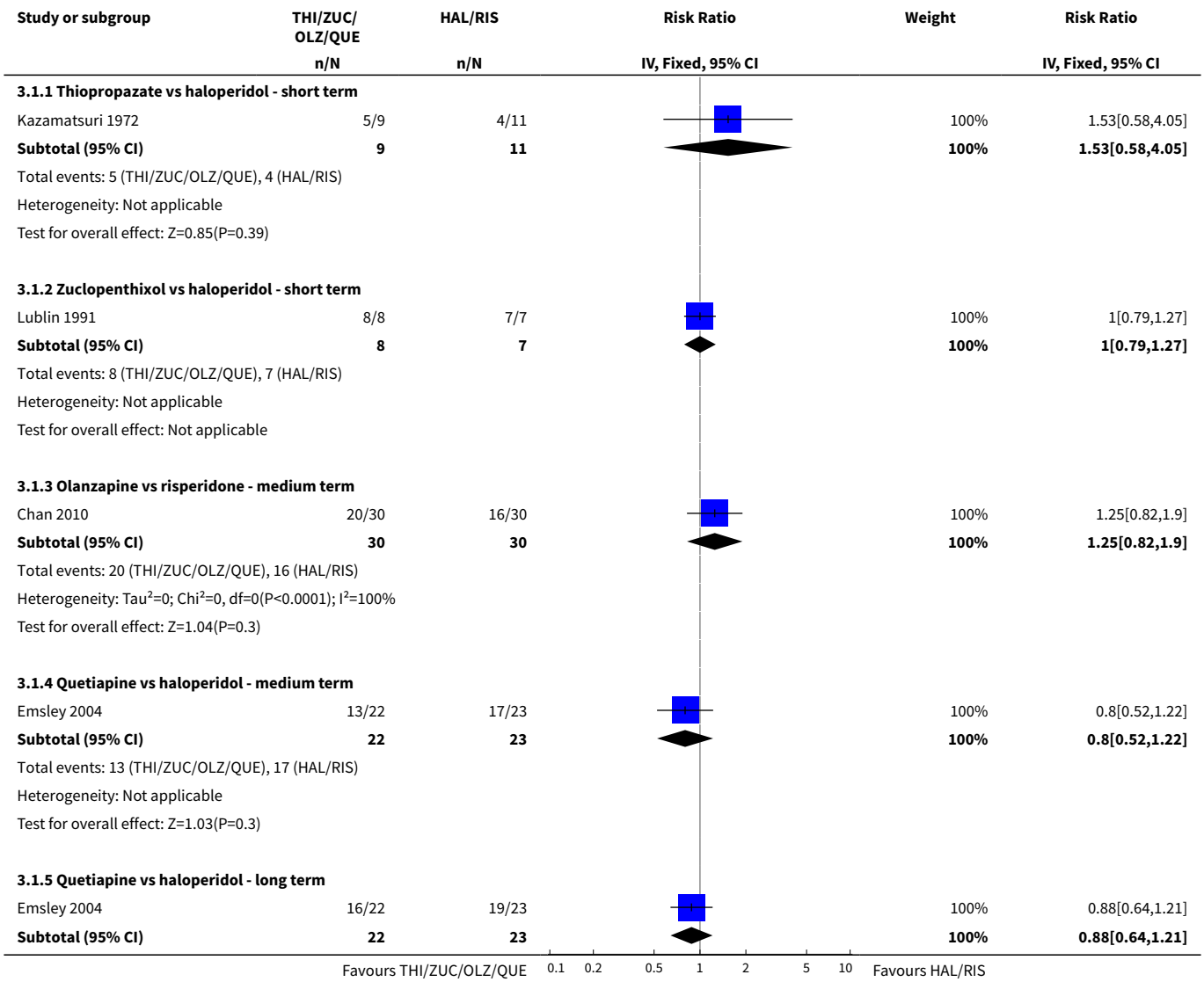
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Olanzapine vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	1.66 [-0.45, 3.77]
5.2 Amisulpride vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-2.85, 1.21]
5.3 Olanzapine vs amisulpride	1	54	Mean Difference (IV, Fixed, 95% CI)	2.48 [0.44, 4.52]
5.4 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.58, 4.98]
6 General mental state: deterioration	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Zuclopenthixol vs haloperidol - short term	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 6.29]
6.2 Olanzapine vs risperidone - medium term	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.64]
6.3 Quetiapine vs haloperidol - long term	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.62, 5.39]
7 General mental state: average endpoint score (PANSS-general psychopathology, low = better) (long term)	1	45	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-6.02, 1.62]
7.1 Quetiapine vs haloperidol	1	45	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-6.02, 1.62]
8 General mental state: average change score (BPRS, low = better) (medium term)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Olanzapine vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-4.79, 2.51]
8.2 Amisulpride vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-2.46 [-6.27, 1.35]
8.3 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-8.37, 4.97]
8.4 Olanzapine vs amisulpride	1	54	Mean Difference (IV, Fixed, 95% CI)	1.32 [-1.94, 4.58]
9 Acceptability of the treatment: leaving the study early (short term)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Molindone vs haloperidol	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

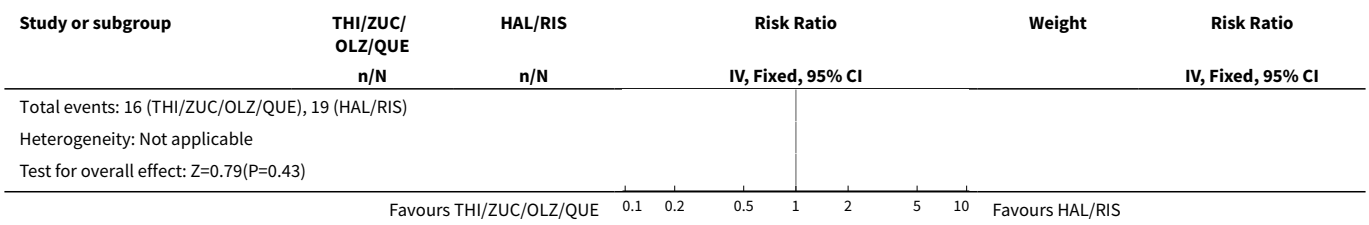
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Thiopropazate vs haloperidol	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.01, 4.44]
10 Acceptability of the treatment: leaving the study early (medium term)	3		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
10.1 Olanzapine vs FGA	1	56	Risk Ratio (IV, Fixed, 95% CI)	1.86 [0.18, 19.38]
10.2 Amisulpride vs FGA	1	55	Risk Ratio (IV, Fixed, 95% CI)	0.96 [0.06, 14.65]
10.3 Olanzapine vs amisulpride	1	57	Risk Ratio (IV, Fixed, 95% CI)	1.93 [0.19, 20.12]
10.4 Olanzapine vs risperidone	2	170	Risk Ratio (IV, Fixed, 95% CI)	0.73 [0.57, 0.95]
10.5 Olanzapine vs quetiapine	1	116	Risk Ratio (IV, Fixed, 95% CI)	0.70 [0.54, 0.90]
10.6 Olanzapine vs ziprasidone	1	82	Risk Ratio (IV, Fixed, 95% CI)	0.77 [0.56, 1.05]
10.7 Quetiapine vs risperidone	1	118	Risk Ratio (IV, Fixed, 95% CI)	1.05 [0.88, 1.25]
10.8 Quetiapine vs ziprasidone	1	90	Risk Ratio (IV, Fixed, 95% CI)	1.10 [0.86, 1.40]
10.9 Ziprasidone vs risperidone	1	84	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.74, 1.23]
11 Acceptability of the treatment: leaving the study early (long term)	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
11.1 Clozapine vs haloperidol	1	39	Risk Ratio (IV, Fixed, 95% CI)	3.36 [0.45, 25.16]
11.2 Quetiapine vs haloperidol	1	45	Risk Ratio (IV, Fixed, 95% CI)	1.31 [0.63, 2.69]
12 Adverse events: extrapyramidal symptoms (need of antiparkinsonism drugs)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Risperidone vs haloperidol (medium term)	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.34, 1.35]
12.2 Quetiapine vs haloperidol (long term)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.21, 0.96]
13 Adverse effects: parkinsonism (SHRS) - average endpoint scores (short term)	1	15	Mean Difference (IV, Fixed, 95% CI)	-4.81 [-12.15, 2.53]
13.1 Zuclopenthixol vs haloperidol	1	15	Mean Difference (IV, Fixed, 95% CI)	-4.81 [-12.15, 2.53]
14 Adverse effects: parkinsonism (SAS, ESRS, low = better) - average change score (medium term)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Olanzapine vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.85 [-2.55, 0.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Amisulpride vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.45, 1.45]
14.3 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-1.33, -0.07]
14.4 Olanzapine vs amisulpride	1	54	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-2.44, 1.74]
15 Adverse effects: dyskinesia (ESRS, low = better) - average change score (medium term)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.91, 1.51]
16 Adverse effects: akathisia (BAS, ESRS, low = better) - average change scores (medium term)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 Olanzapine vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.30, 0.46]
16.2 Amisulpride vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.42, 0.20]
16.3 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.8 [-1.76, 0.16]
16.4 Olanzapine vs amisulpride	1	54	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.12, 0.50]
17 Adverse effects: dystonia (ESRS, low = better) - average change score (medium term)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-1.41, 0.01]
18 Adverse effects: general adverse events (UKU, low = better) - average change score (medium term)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 Olanzapine vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	0.08 [-1.85, 2.01]
18.2 Amisulpride vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-2.33, 1.23]
18.3 Olanzapine vs amisulpride	1	54	Mean Difference (IV, Fixed, 95% CI)	0.63 [-0.93, 2.19]
19 General global state: average change score (CGI) (medium term)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

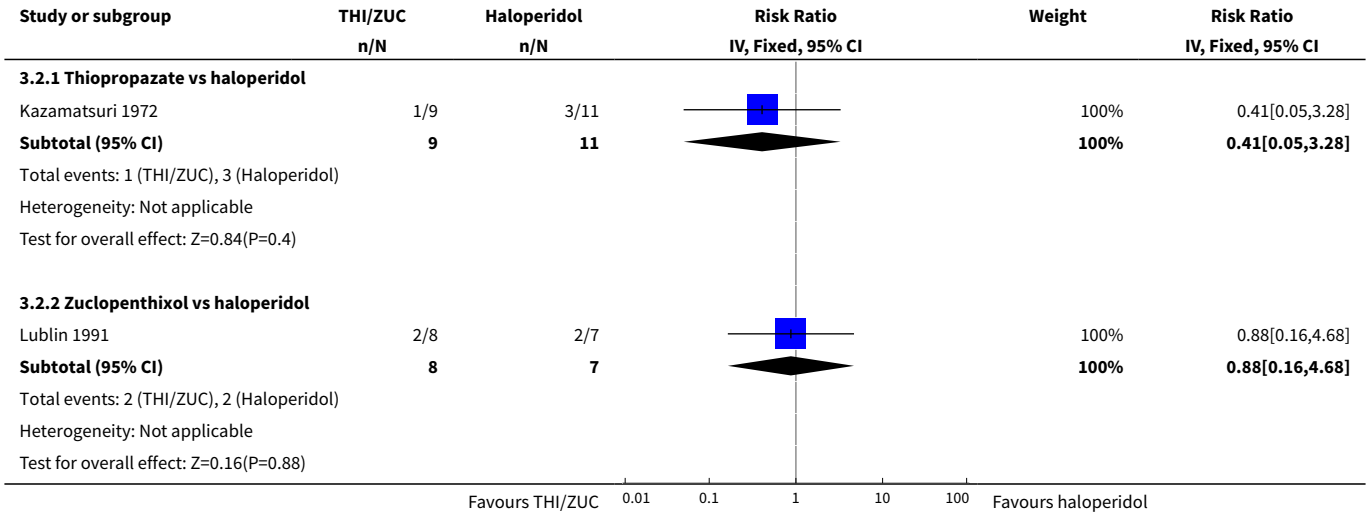
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Olanzapine vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.41, 0.27]
19.2 Amisulpride vs FGA	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.47, 0.09]
19.3 Olanzapine vs risperidone	1	60	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.61, 0.81]
19.4 Olanzapine vs amisulpride	1	54	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.19, 0.43]

Analysis 3.1. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 1 Tardive dyskinesia: no clinically important improvement.

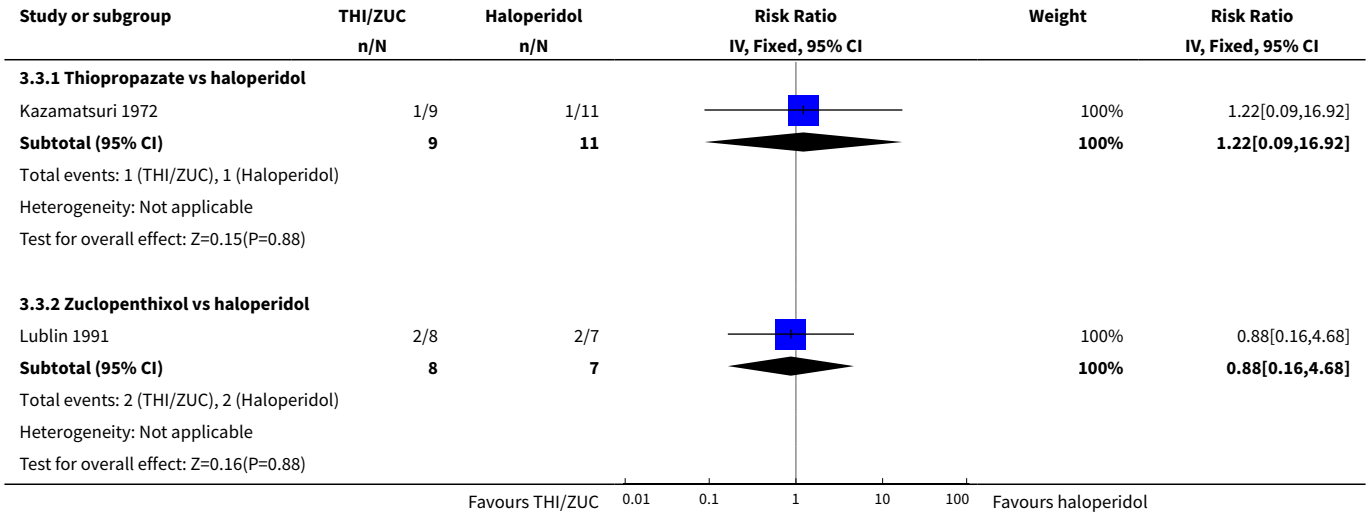




Analysis 3.2. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 2 Tardive dyskinesia: not any improvement (short term).

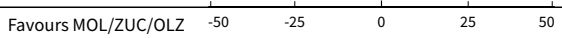


Analysis 3.3. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 3 Tardive dyskinesia: deterioration (short term).



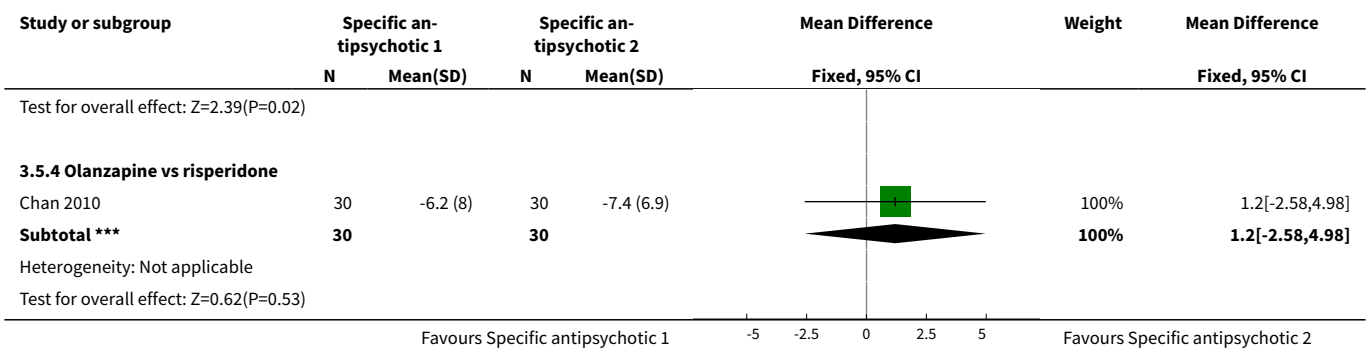
Analysis 3.4. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 4 Tardive dyskinesia: average endpoint score (various scales).

Study or subgroup	MOL/ZUC/OLZ N	MOL/ZUC/OLZ Mean(SD)	HAL/RIS N	HAL/RIS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.4.1 Molindone vs haloperidol, 100% masking dose (AIMS, short term)							
Glazer 1990a	9	9.9 (2.2)	9	8.1 (2.3)		100%	1.87[-0.2,3.94]
Subtotal ***	**9**		**9**			**100%**	**1.87[-0.2,3.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.77(P=0.08)							
3.4.2 Molindone vs haloperidol, 200% masking dose (AIMS, short term)							
Glazer 1990a	9	8.7 (2.9)	9	5.2 (2.1)		100%	3.44[1.12,5.76]
Subtotal ***	**9**		**9**			**100%**	**3.44[1.12,5.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.91(P=0)							
3.4.3 Zuclopenthixol vs haloperidol (SHRS, short term)							
Lublin 1991	8	10.5 (9.8)	7	15.3 (3.9)		100%	-4.81[-12.15,2.53]
Subtotal ***	**8**		**7**			**100%**	**-4.81[-12.15,2.53]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.28(P=0.2)							
3.4.4 Olanzapine vs risperidone (AIMS, medium term)							
Chan 2010	30	19.4 (6.1)	30	17.2 (4.6)		100%	2.2[-0.53,4.93]
Subtotal ***	**30**		**30**			**100%**	**2.2[-0.53,4.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.58(P=0.11)							

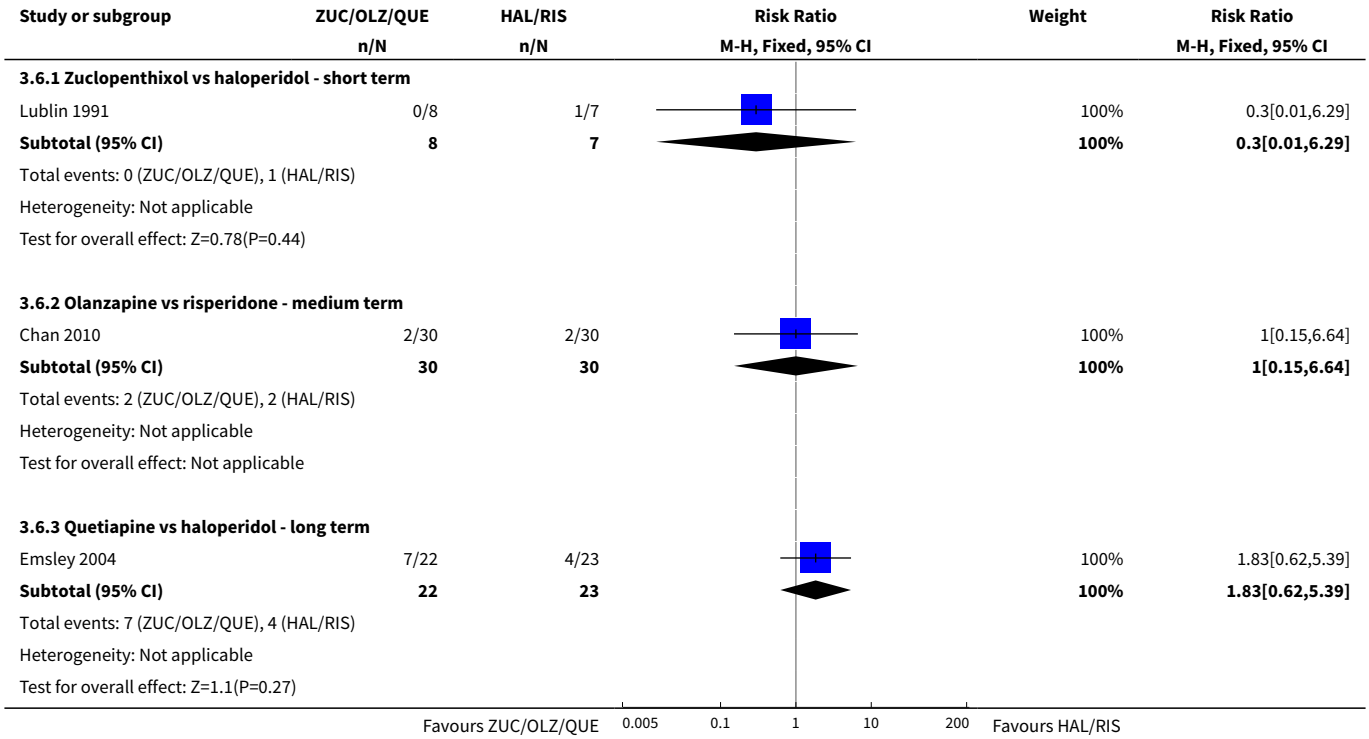


Analysis 3.5. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 5 Tardive dyskinesia: average change score (AIMS, low = better) (medium term).

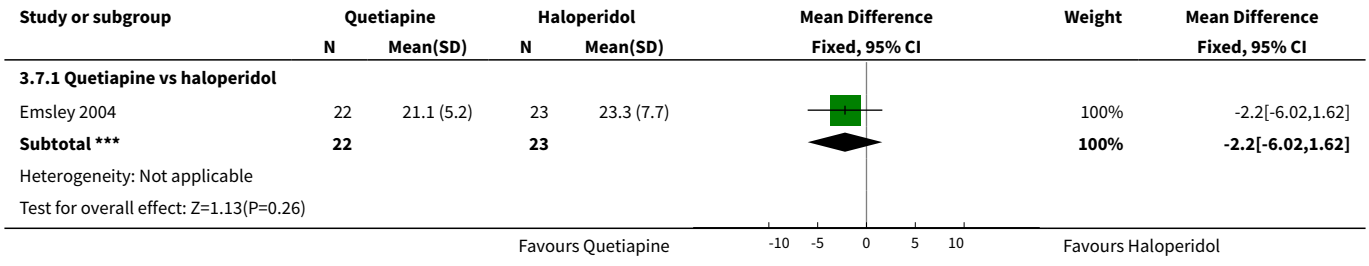
Study or subgroup	Specific antipsychotic 1 N	Specific antipsychotic 1 Mean(SD)	Specific antipsychotic 2 N	Specific antipsychotic 2 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.5.1 Olanzapine vs FGA							
Bai 2005	27	-0.1 (4)	26	-1.8 (3.9)		100%	1.66[-0.45,3.77]
Subtotal ***	**27**		**26**			**100%**	**1.66[-0.45,3.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							
3.5.2 Amisulpride vs FGA							
Bai 2005	27	-2.6 (3.7)	26	-1.8 (3.9)		100%	-0.82[-2.85,1.21]
Subtotal ***	**27**		**26**			**100%**	**-0.82[-2.85,1.21]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.79(P=0.43)							
3.5.3 Olanzapine vs amisulpride							
Bai 2005	27	-0.1 (4)	27	-2.6 (3.7)		100%	2.48[0.44,4.52]
Subtotal ***	**27**		**27**			**100%**	**2.48[0.44,4.52]**
Heterogeneity: Not applicable							

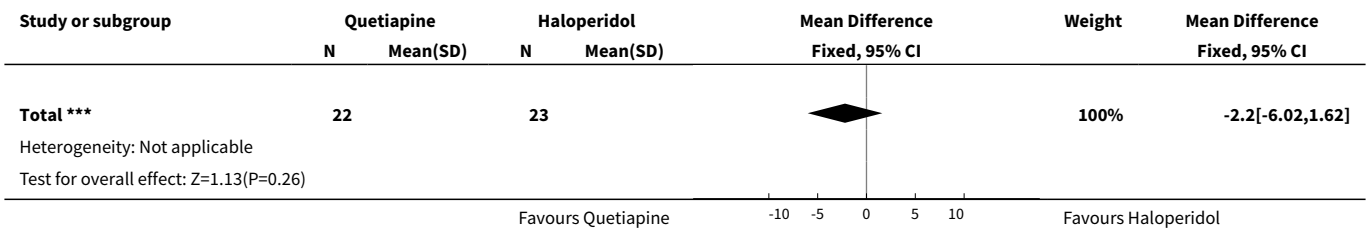


Analysis 3.6. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 6 General mental state: deterioration.

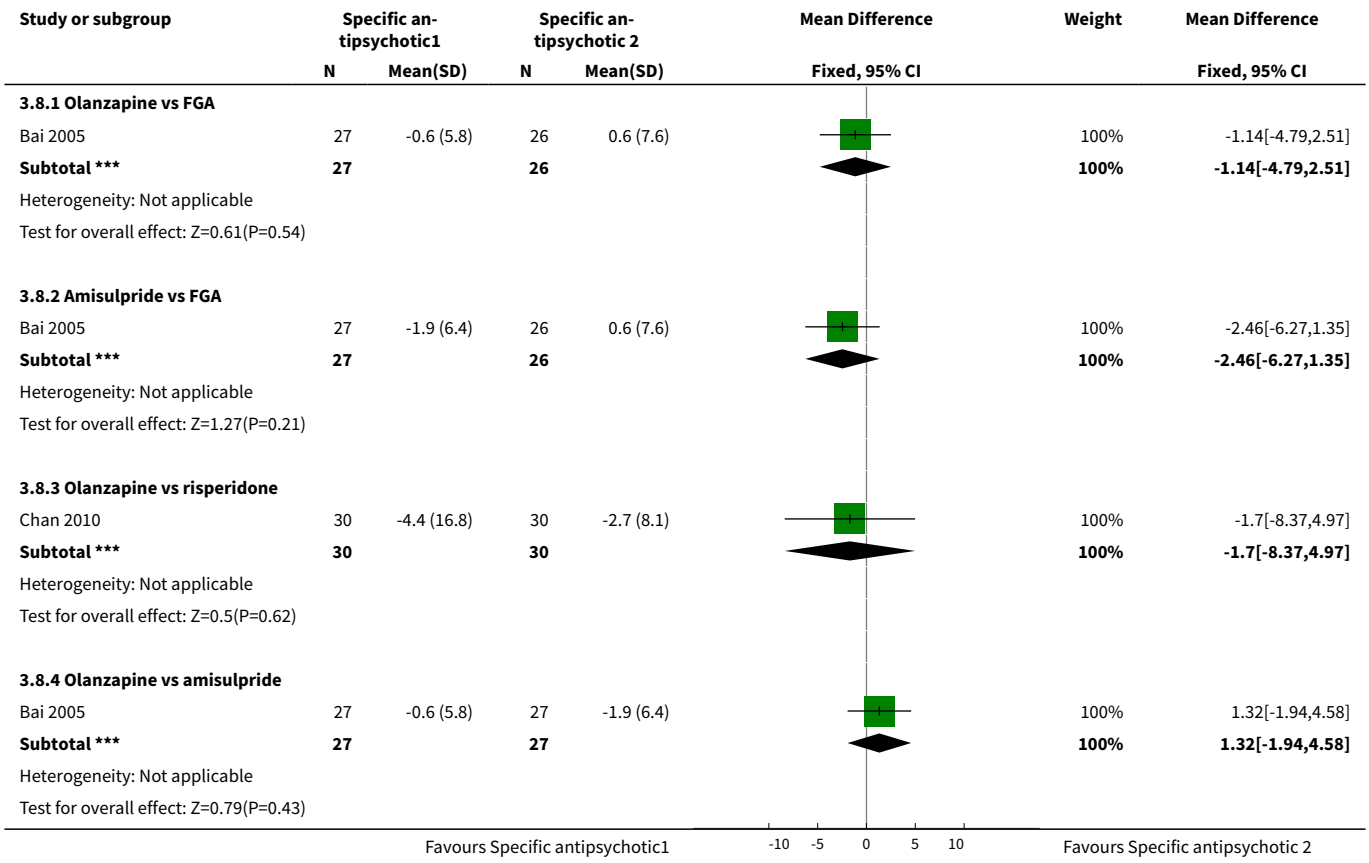


Analysis 3.7. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 7 General mental state: average endpoint score (PANSS-general psychopathology, low = better) (long term).

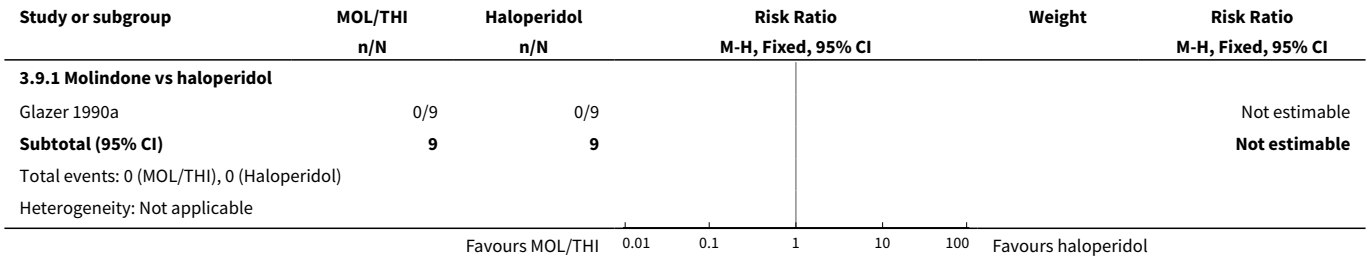


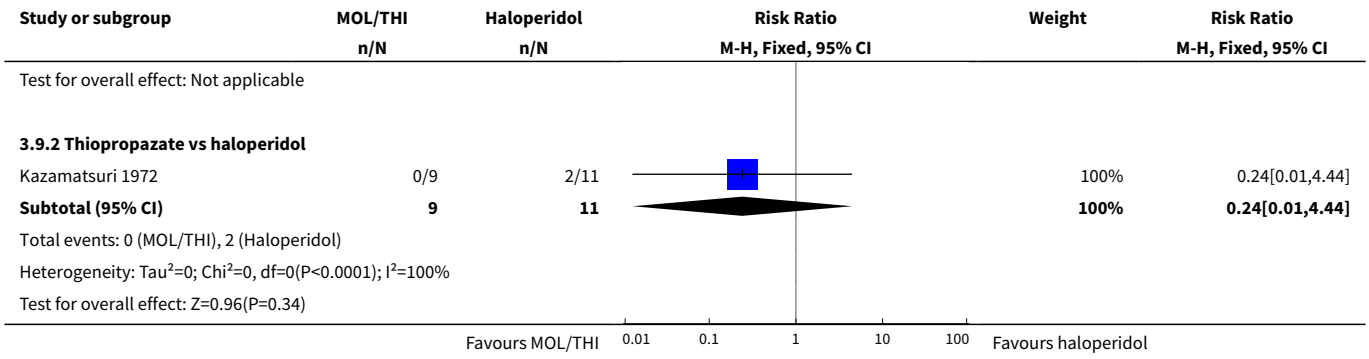


Analysis 3.8. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 8 General mental state: average change score (BPRS, low = better) (medium term).

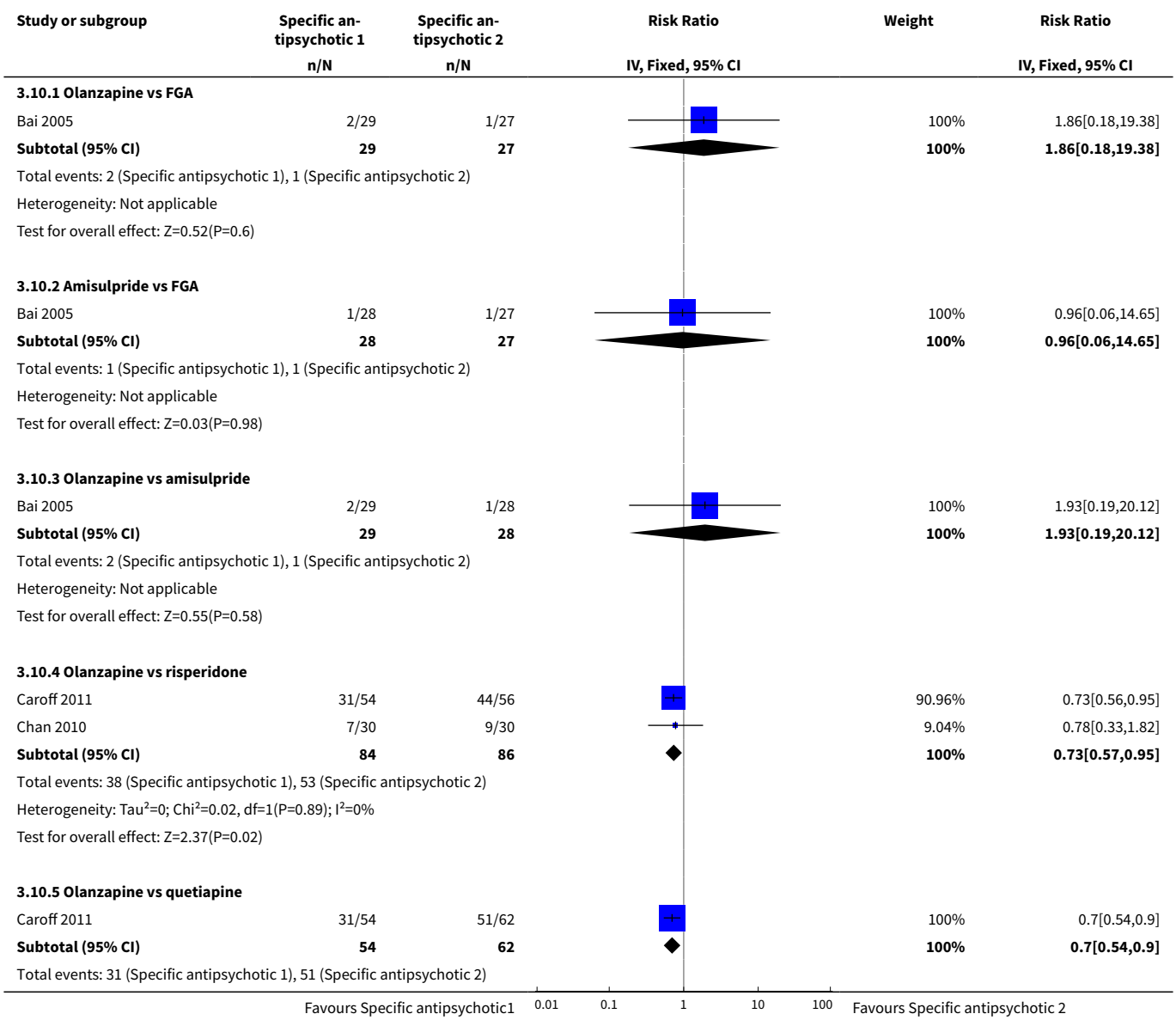


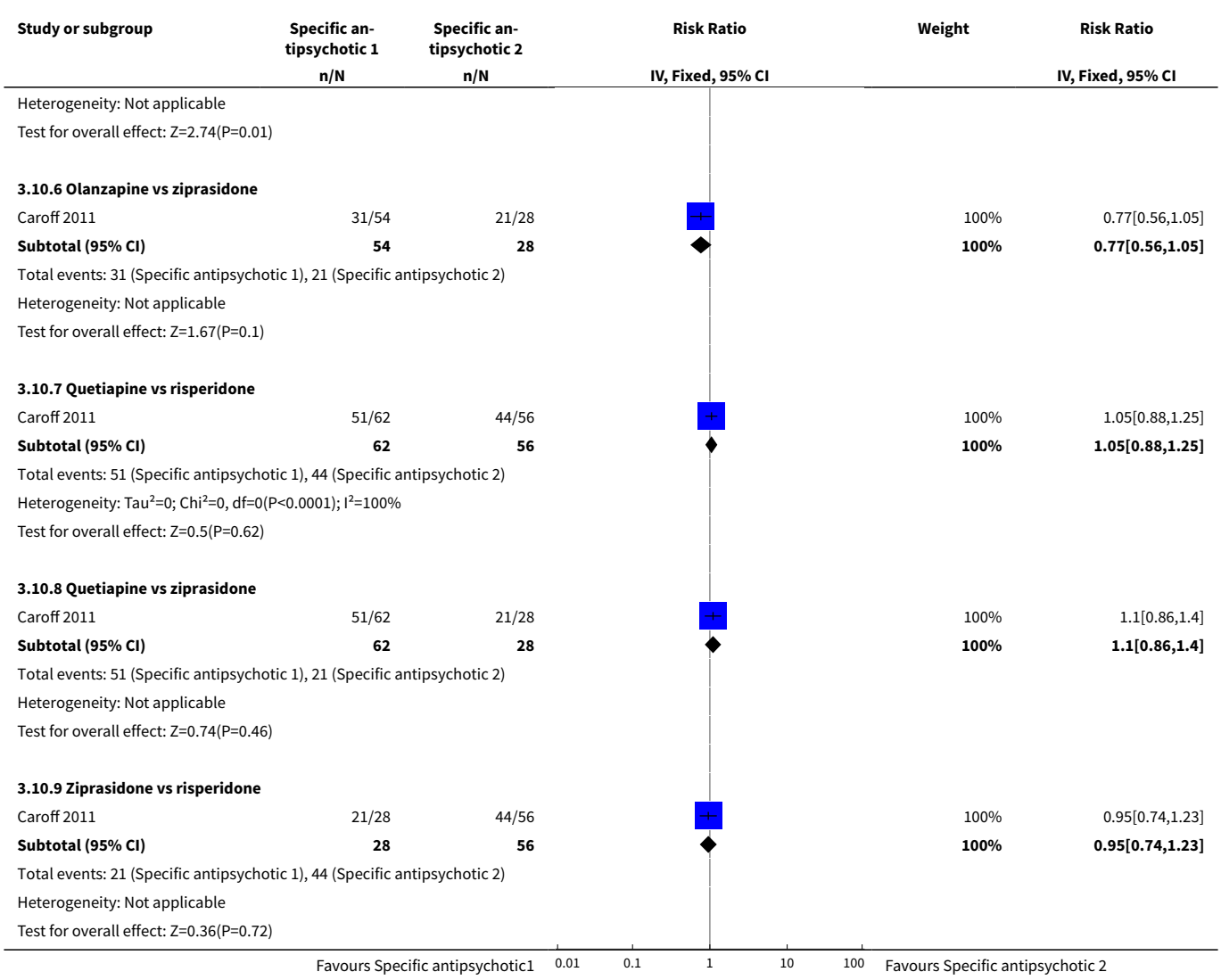
Analysis 3.9. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 9 Acceptability of the treatment: leaving the study early (short term).



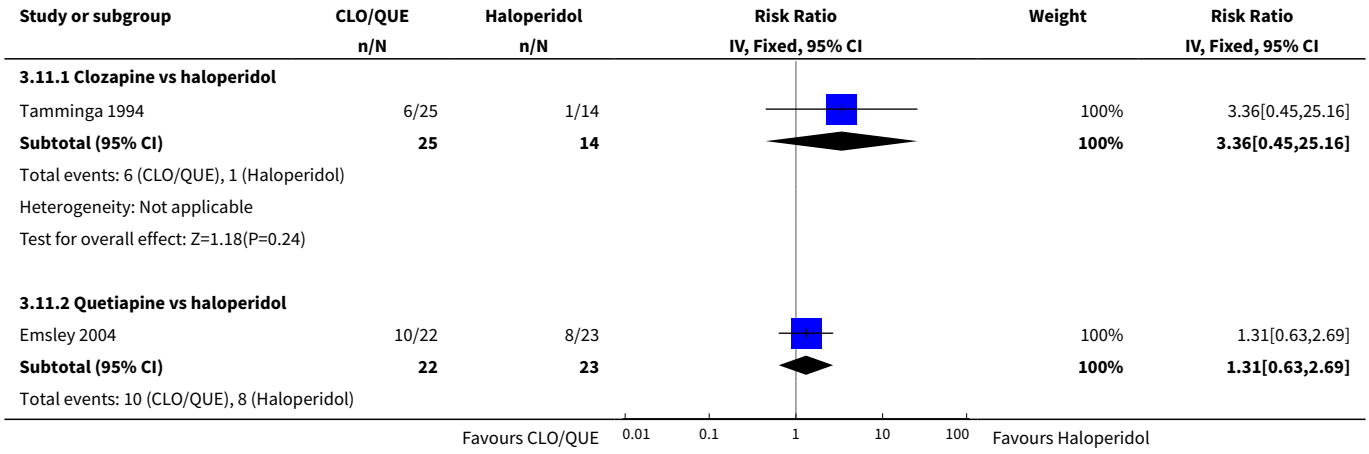


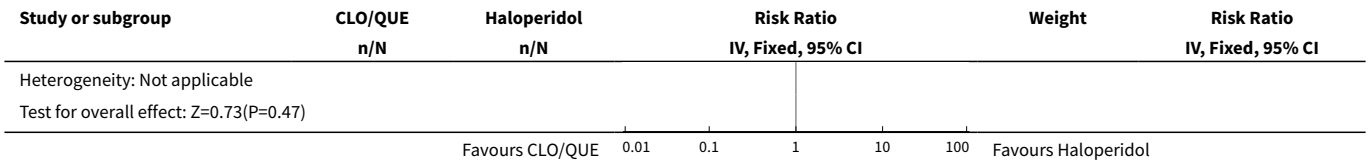
Analysis 3.10. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 10 Acceptability of the treatment: leaving the study early (medium term).



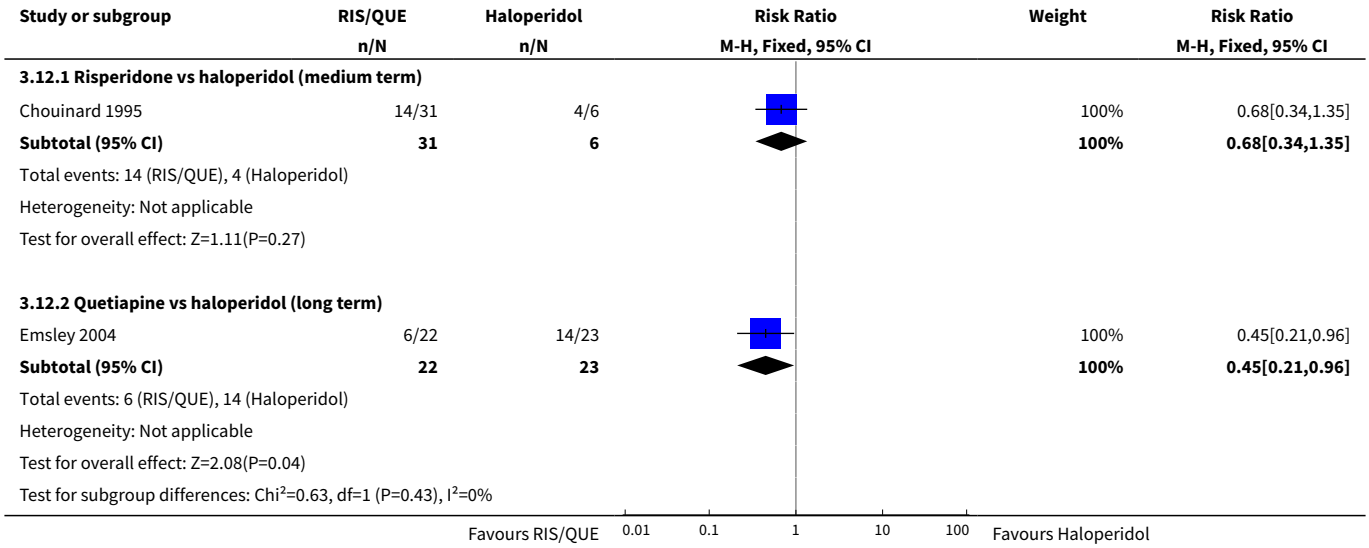


Analysis 3.11. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 11 Acceptability of the treatment: leaving the study early (long term).

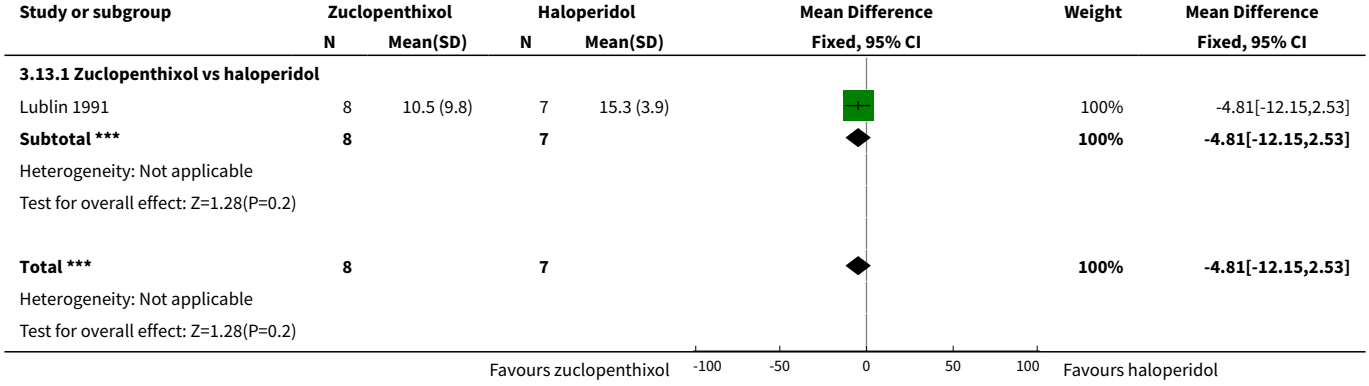




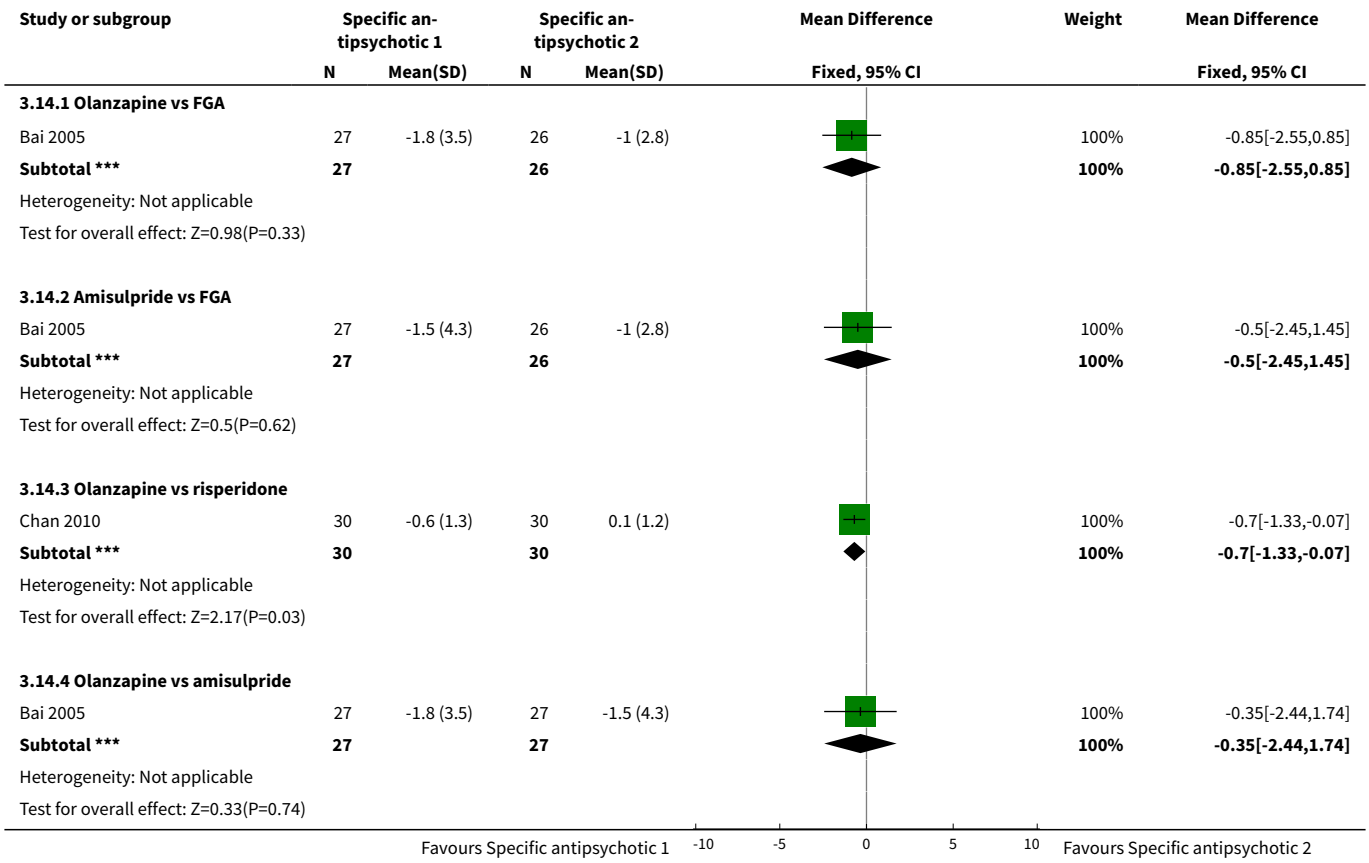
Analysis 3.12. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 12 Adverse events: extrapyramidal symptoms (need of antiparkinsonism drugs).



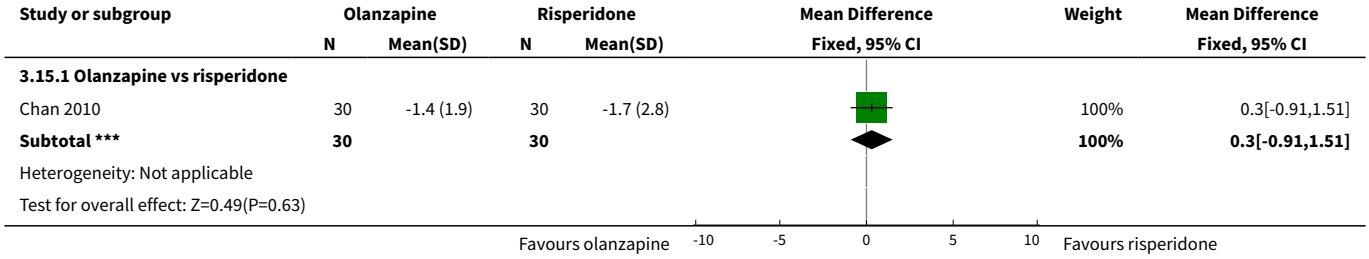
Analysis 3.13. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 13 Adverse effects: parkinsonism (SHRS) - average endpoint scores (short term).



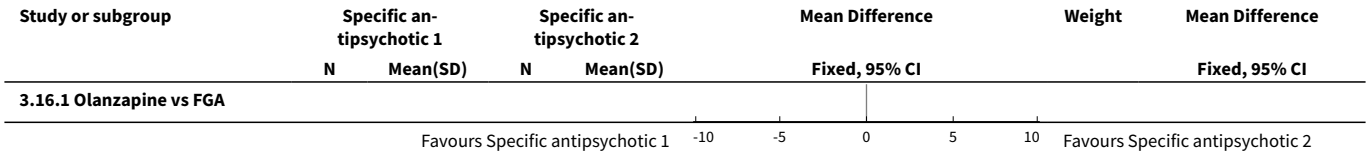
Analysis 3.14. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 14 Adverse effects: parkinsonism (SAS, ESRS, low = better) - average change score (medium term).

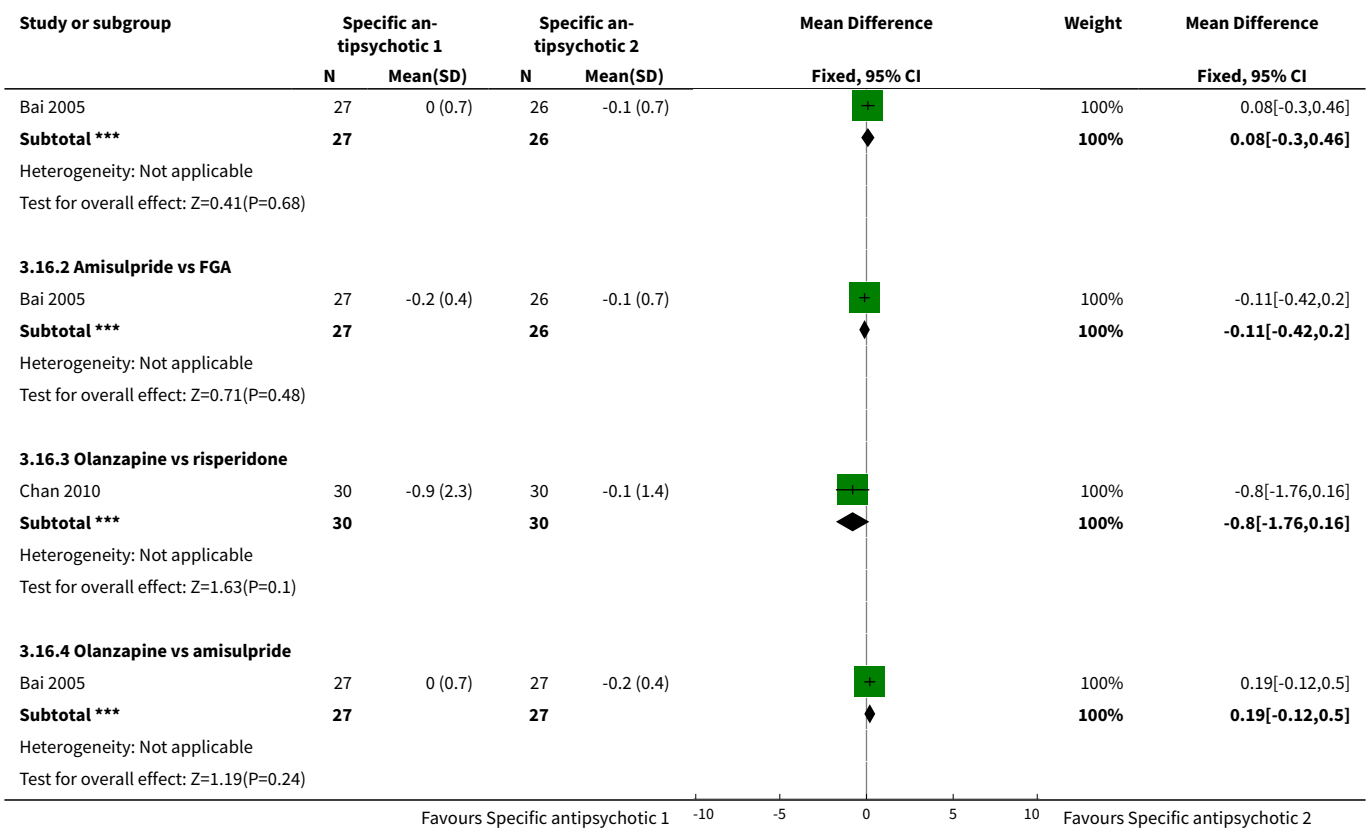


Analysis 3.15. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 15 Adverse effects: dyskinesia (ESRS, low = better) - average change score (medium term).

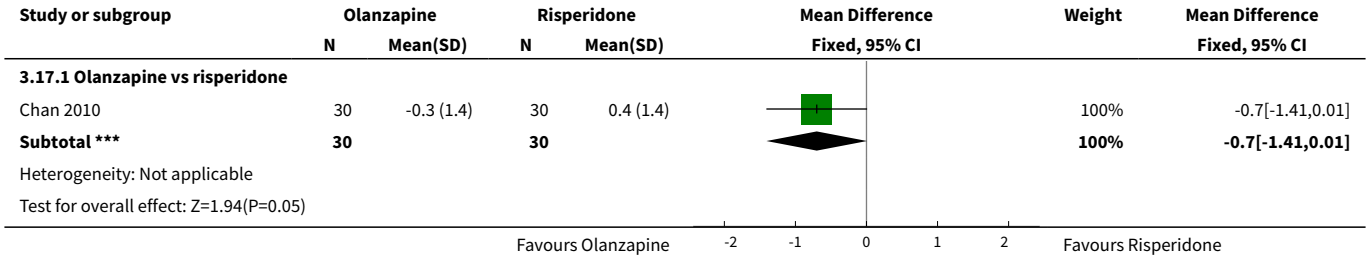


Analysis 3.16. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 16 Adverse effects: akathisia (BAS, ESRS, low = better) - average change scores (medium term).

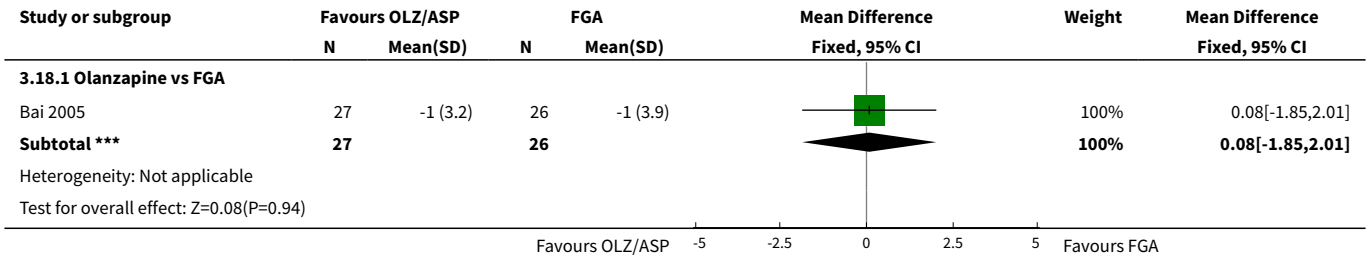


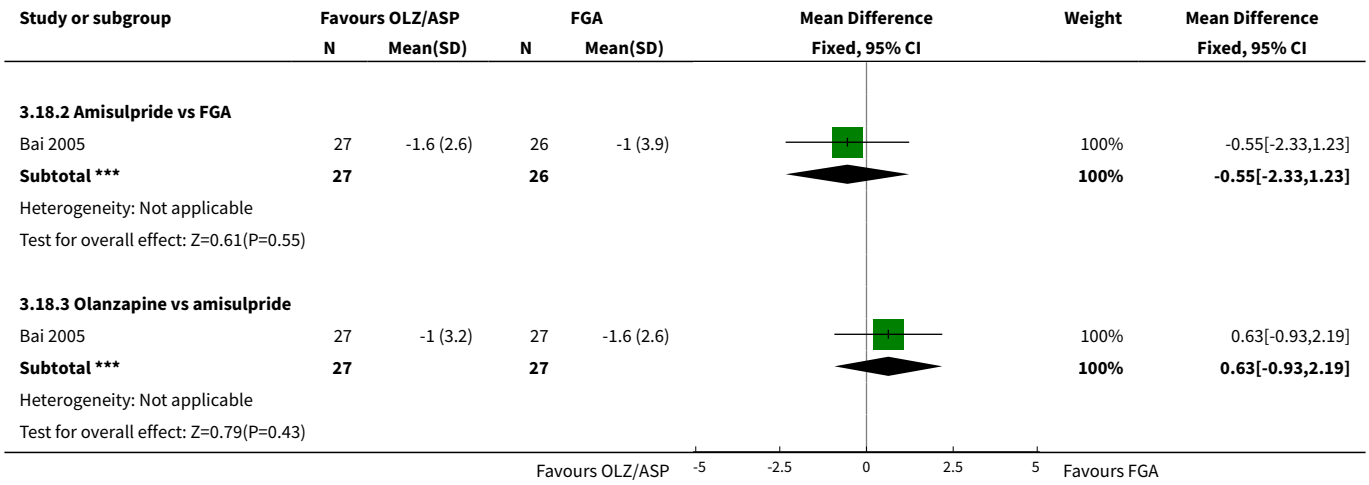


Analysis 3.17. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 17 Adverse effects: dystonia (ESRS, low = better) - average change score (medium term).

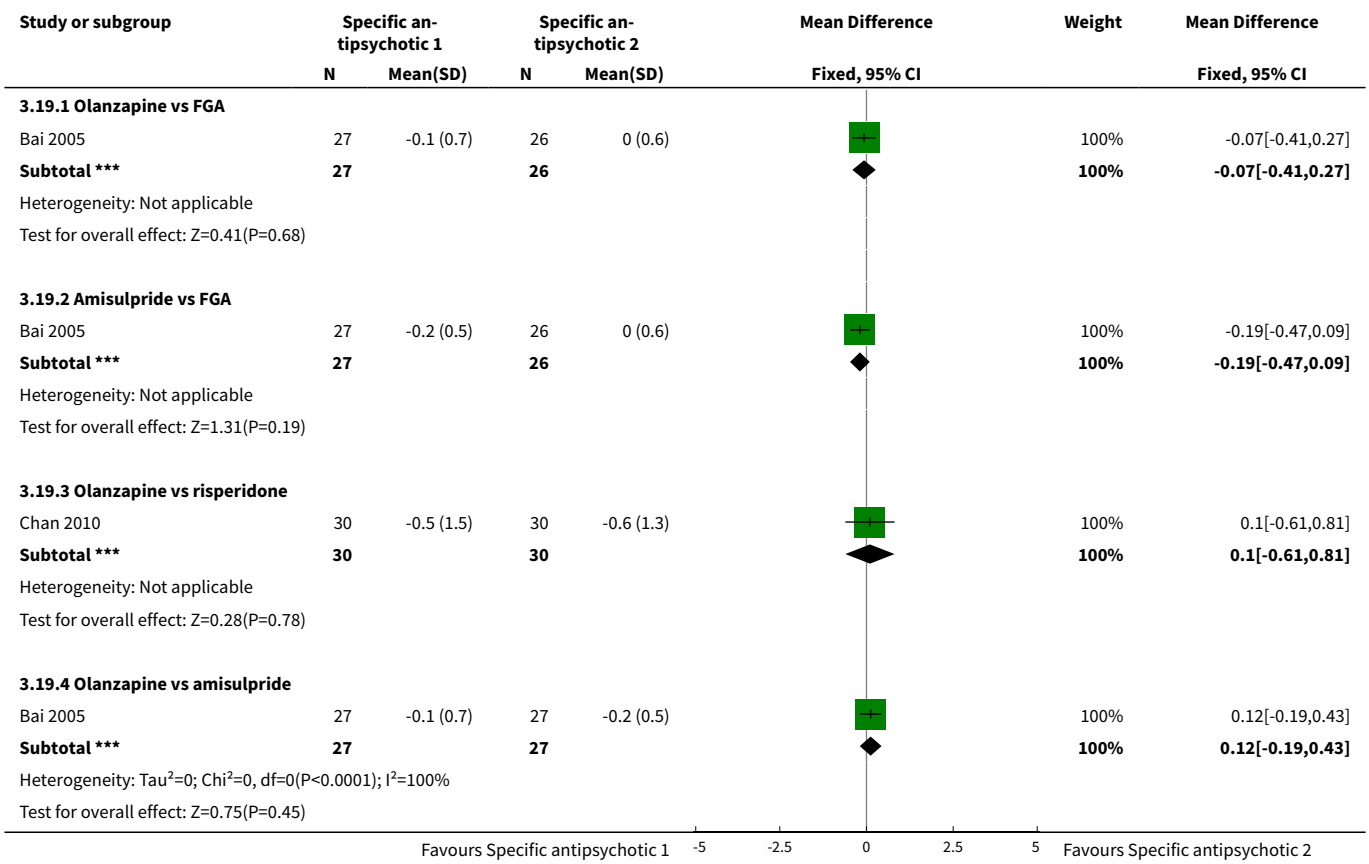


Analysis 3.18. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 18 Adverse effects: general adverse events (UKU, low = better) - average change score (medium term).





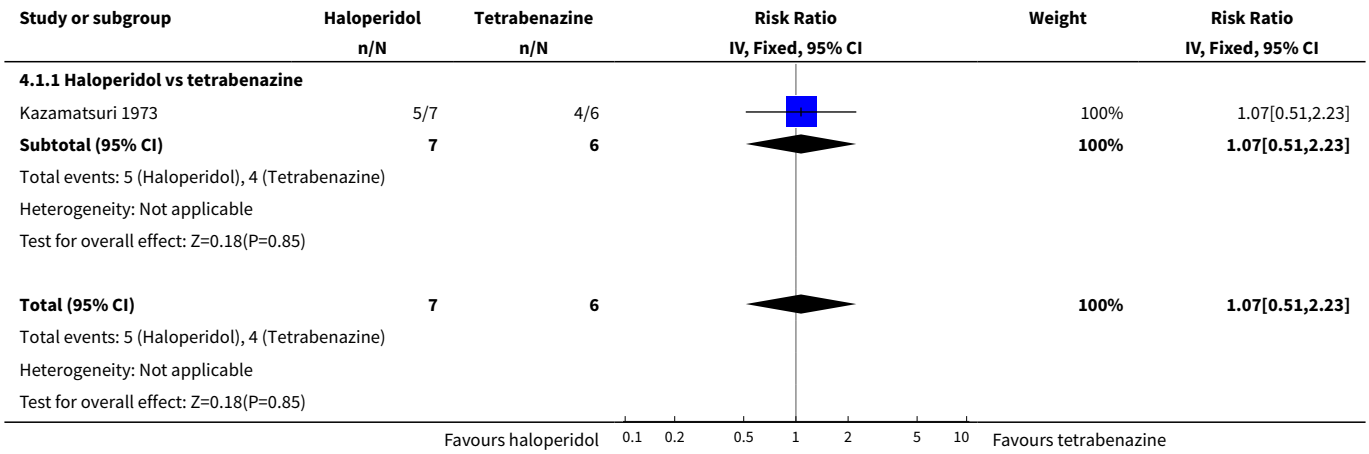
Analysis 3.19. Comparison 3 Switch to a specific antipsychotic vs switch to a different antipsychotic, Outcome 19 General global state: average change score (CGI) (medium term).



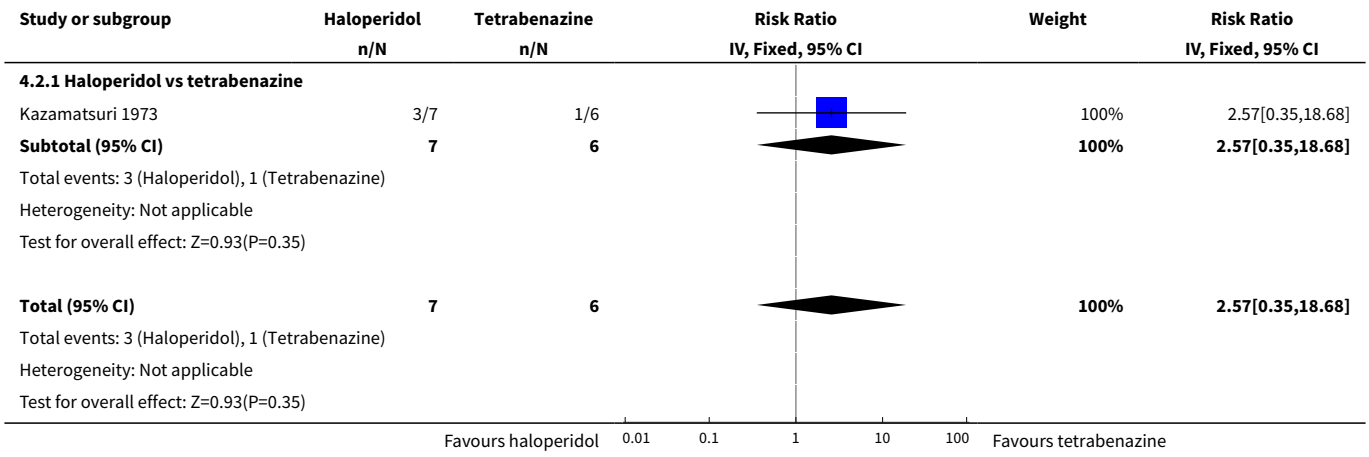
Comparison 4. Specific antipsychotic vs other drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesias: no clinically important improvement (medium term)	1	13	Risk Ratio (IV, Fixed, 95% CI)	1.07 [0.51, 2.23]
1.1 Haloperidol vs tetrabenazine	1	13	Risk Ratio (IV, Fixed, 95% CI)	1.07 [0.51, 2.23]
2 Tardive dyskinesia: no improvement (medium term)	1	13	Risk Ratio (IV, Fixed, 95% CI)	2.57 [0.35, 18.68]
2.1 Haloperidol vs tetrabenazine	1	13	Risk Ratio (IV, Fixed, 95% CI)	2.57 [0.35, 18.68]
3 Tardive dyskinesia: deterioration (medium term)	1	13	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.07, 10.96]
3.1 Haloperidol vs tetrabenazine	1	13	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.07, 10.96]
4 Acceptability of the treatment: leaving the study early (medium term)	1	13	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [0.25, 76.54]
4.1 Haloperidol vs tetrabenazine	1	13	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [0.25, 76.54]

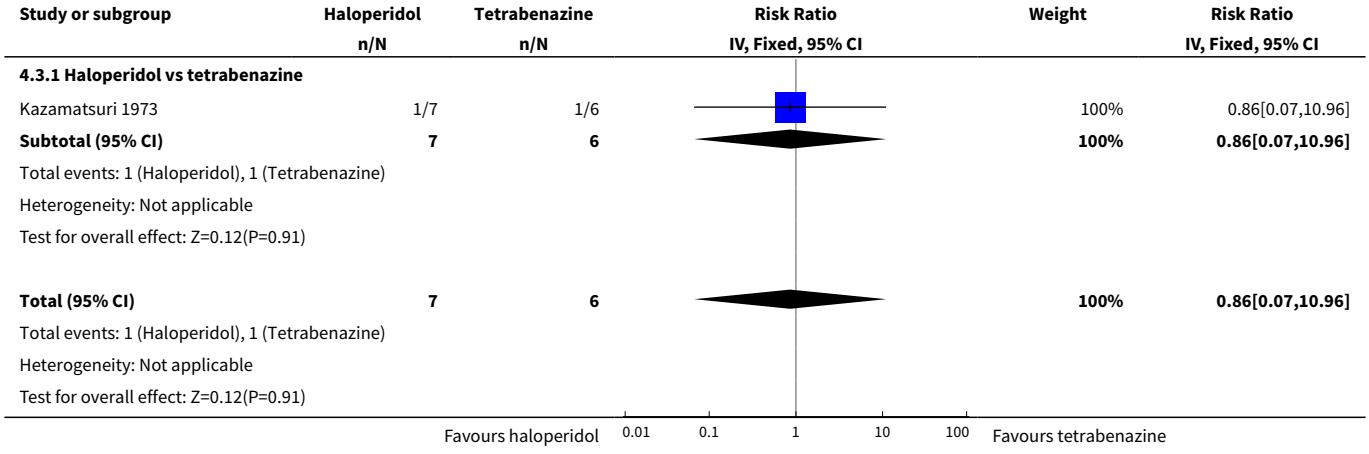
Analysis 4.1. Comparison 4 Specific antipsychotic vs other drugs, Outcome 1 Tardive dyskinesias: no clinically important improvement (medium term).



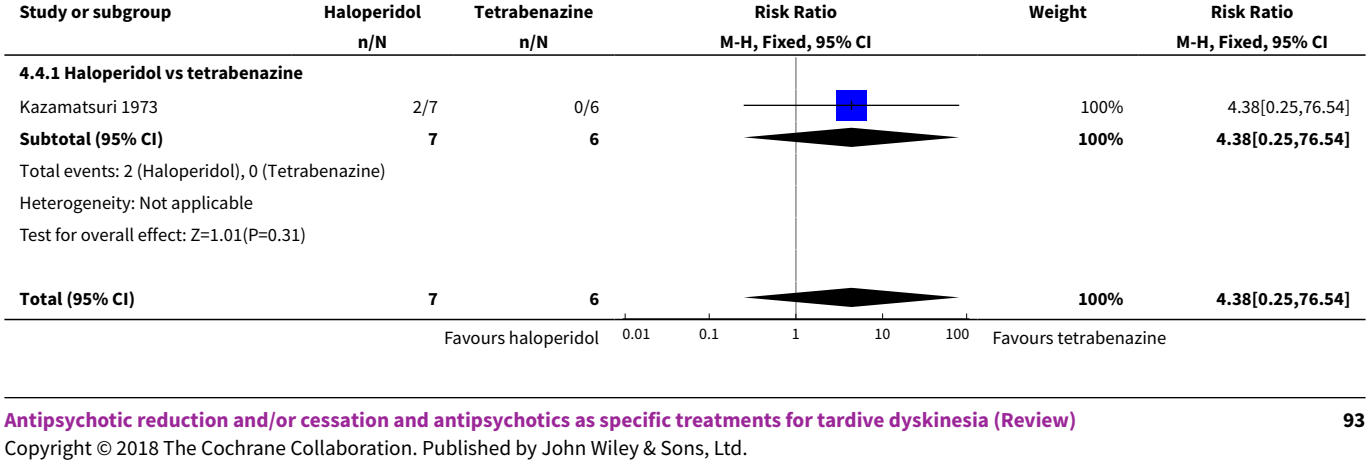
Analysis 4.2. Comparison 4 Specific antipsychotic vs other drugs, Outcome 2 Tardive dyskinesia: no improvement (medium term).

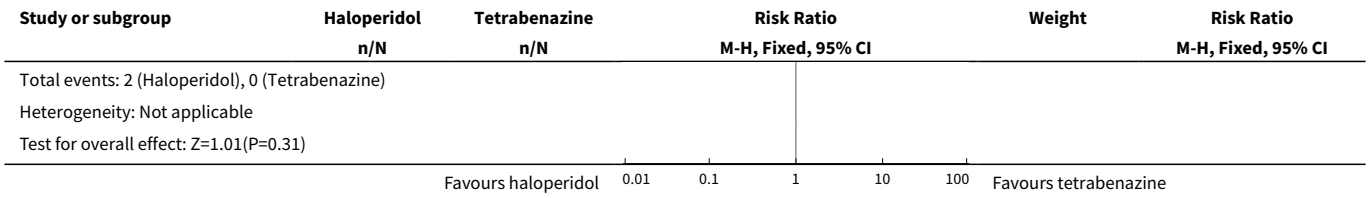


Analysis 4.3. Comparison 4 Specific antipsychotic vs other drugs, Outcome 3 Tardive dyskinesia: deterioration (medium term).



Analysis 4.4. Comparison 4 Specific antipsychotic vs other drugs, Outcome 4 Acceptability of the treatment: leaving the study early (medium term).





ADDITIONAL TABLES

Table 2. Excluded studies relevant to schizophrenia: comparisons for existing or potential reviews

Study ID	Participants – people with:	Intervention	Comparison for review	Cochrane Review
Cai 1988	Tardive dyskinesia	1-stepholidine vs placebo	1-stepholidine for schizophrenia	-
Speller 1997	Schizophrenia	Amisulpride vs haloperidol	Amisulpride versus haloperidol for schizophrenia	
Gerlach 1978	Tardive dyskinesia	Biperiden vs no treatment	Anticholinergic drugs for tardive dyskinesia	
NDSG 1986		Chlorprothixene versus haloperidol vs perphenazine vs haloperidol + biperiden		
Greil 1984		Biperiden vs placebo		
Chouinard 1979	Schizophrenia	Ethopropazine vs benztropine	Anticholinergics for parkinsonism	
Spohn 1988		Abrupt neuroleptic cessation vs neuroleptic maintenance	Antipsychotic reduction or withdrawal for schizophrenia	
Spohn 1993		Abrupt neuroleptic cessation vs neuroleptic maintenance		
Wistedt 1983		Fluphenazine/flupenthixol decanoate continuation vs withdrawal		
Goldberg 1981		Withdrawal of fluphenazine decanoate vs continuation		
Hershon 1972		Trifluoperazine withdrawal vs trifluoperazine continuation		
Johnson 1987		Dose reduction vs maintenance (both arms used flupenthixol decanoate)		
Kinon 2004		Olanzapine with different timings of dose-reduction periods		
Levine 1980		Fluphenazine withdrawal vs continuation		

Table 2. Excluded studies relevant to schizophrenia: comparisons for existing or potential reviews *(Continued)*

Marder 1987		Low- vs conventional-dose maintenance therapy with fluphenazine decanoate		
Newcomer 1992		Haloperidol dose reduction vs maintained dose		
Singh 1990		Abrupt neuroleptic cessation vs neuroleptic maintenance		
Zeng 1994	Tardive dyskinesia	Flunarizine vs placebo	Calcium channel blockers for neuroleptic-induced tardive dyskinesia	
Jeste 1977	Schizophrenia	Chlorpromazine schedule A vs chlorpromazine schedule B	Chlorpromazine timing of dose for schizophrenia.	
NDSG 1986	Tardive dyskinesia	Chlorprothixene vs haloperidol vs perphenazine vs haloperidol + biperiden	Chlorprothixene for schizophrenia.	
Andia 1998	Schizophrenia	Clozapine vs haloperidol	Clozapine versus haloperidol for schizophrenia	
Gerlach 1975		Clozapine vs haloperidol		
Bitter 2000		Clozapine vs olanzapine	Clozapine versus olanzapine for schizophrenia	
Jean-Noel 1999		Clozapine vs olanzapine		
Caine 1979	Gilles de la Tourette's, Huntington's disease and drug-induced atypical dyskinesia	Clozapine vs placebo	Clozapine versus placebo for schizophrenia.	
Chouinard 1994	Schizophrenia	Clozapine versus risperidone	Clozapine versus risperidone for schizophrenia	
Chouinard 1989		Haloperidol decanoate vs fluphenazine decanoate	Depot fluphenazine for schizophrenia	
Cookson 1991		Fluphenazine decanoate vs haloperidol decanoate		
Curson 1985		Fluphenazine decanoate vs placebo		
McCreadie 1980		Fluphenazine decanoate vs intermittent pimozide		
Odejide 1982		Fluphenazine decanoate vs vitamin B complex		
Chouinard 1978		Fluphenazine ethanoate vs pipothiazine palmitate		
Chouinard 1989, Cookson 1991		Haloperidol decanoate vs fluphenazine decanoate	Depot haloperidol decanoate for schizophrenia.	

Table 2. Excluded studies relevant to schizophrenia: comparisons for existing or potential reviews *(Continued)*

Chouinard 1978		Fluphenazine ethanoate vs pipothiazine palmitate	Depot pipothiazine for schizophrenia.
Burner 1989		Progabide vs placebo	GABA for schizophrenia
Bateman 1979	Tardive dyskinesia and psychiatric history	Metoclopramide (10 mg, 20 mg or 40 mg) vs haloperidol (5 mg or 10 mg)	Haloperdiol dose for schizophrenia
Tran 1997, Rosenheck 2003, Tollefson 1997	Schizophrenia	Haloperidol vs olanzapine	Haloperidol vs olanzapine for schizophrenia
NDSG 1986	Tardive dyskinesia	Chlorprothixene vs haloperidol vs perphenazine vs haloperidol + biperiden	Haloperidol vs perphenazine for schizophrenia
Kopala 2004, Wirshing 1999	Schizophrenia	Haloperidol vs risperidone	Haloperidol vs risperidone for schizophrenia
Jolley 1990		Brief intermittent antipsychotic treatment vs fluphenazine decanoate	Intermittent antipsychotic treatment for schizophrenia
McCreadie 1980		Fluphenazine decanoate vs intermittent pimozide	
Newton 1989		Haloperidol with 'drug holiday' vs haloperidol	
Goldberg 1981		Withdrawal of fluphenazine decanoate vs continuation	
MacKay 1980		Lithium vs placebo	Lithium for schizophrenia
Borison 1987		Molidone vs haloperidol	Molidone vs haloperidol for schizophrenia
Williamson 1995		Olanzapine 1 mg vs olanzapine 10 mg versus placebo	Olanzapine dose for schizophrenia.
de Jesus Mari 2004		Olanzapine vs "conventional antipsychotic drugs"	Olanzapine for schizophrenia
Peluso 2012		First-generation antipsychotic vs second-generation antipsychotic	
Kinon 2004		Olanzapine with different timings of dose reduction periods	Olanzapine reduction for schizophrenia
Peluso 2012		First-generation antipsychotic versus second-generation antipsychotic	Olanzapine vs other atypical antipsychotics for schizophrenia
Williamson 1995		Olanzapine 1 mg vs olanzapine 10 mg vs placebo	Olanzapine vs placebo for schizophrenia

Table 2. Excluded studies relevant to schizophrenia: comparisons for existing or potential reviews *(Continued)*

Peluso 2012		First-generation antipsychotic vs second-generation antipsychotic	Perphenazine for schizophrenia
McCreadie 1980		Fluphenazine decanoate vs intermittent pimozide	Pimozide for schizophrenia
Cortese 2008		Quetiapine vs continuation of usual antipsychotic	Quetiapine vs continuation of usual antipsychotic for schizophrenia
Peluso 2012		First generation antipsychotic vs second-generation antipsychotic	Quetiapine vs other atypical antipsychotics for schizophrenia
			Quetiapine vs typical antipsychotic medications for schizophrenia
			Risperidone vs olanzapine for schizophrenia
			Risperidone vs other atypical antipsychotics for schizophrenia
Cortese 2008		Quetiapine vs continuation of usual antipsychotic	Switching antipsychotic for schizophrenia.
Singer 1971	Tardive dyskinesia	Thiopropazate vs placebo	Thiopropazate for schizophrenia
Lal 1974	Schizophrenia	Thiopropazine vs trifluoperazine vs placebo	Thiopropazine vs placebo for schizophrenia
			Thiopropazine vs trifluoperazine for schizophrenia
Delwaide 1979	Tardive dyskinesia	Thioproperazine and tiapride vs placebo	Thioproperazine for schizophrenia
			Tiapride for schizophrenia
Buruma 1982		Tiapride vs placebo	
Crane 1970	Schizophrenia	Trifluoperazine high-dose vs trifluoperazine low-dose vs placebo	Trifluoperazine dose for schizophrenia
			Trifluoperazine vs placebo for schizophrenia
Lal 1974		Thiopropazine vs trifluoperazine vs placebo	
Odejide 1982		Fluphenazine decanoate vs vitamin B complex	Vitamins for schizophrenia

Table 2. Excluded studies relevant to schizophrenia: comparisons for existing or potential reviews *(Continued)*

Peluso 2012	First-generation antipsychotic vs second-generation antipsychotic	Ziprasidone vs other atypical antipsychotics for schizophrenia

Table 3. Suggestions for design of future study

Methods	Allocation: randomised, with sequence generation and concealment of allocation clearly described Blindness: double, tested Duration: 12 months beyond end of intervention at least Raters: independent
Participants	People with antipsychotic-induced tardive dyskinesia[a] Age: any Sex: both History: any N = 300[b]
Interventions	1. Antipsychotic reduction/cessation (N = 150) vs antipsychotic maintenance (N = 150) OR 2. Specific antipsychotic (N = 150) vs other specific antipsychotic (N = 150)
Outcomes	Tardive dyskinesia: any clinically important improvement in tardive dyskinesia, any improvement, deterioration[c] Adverse effects: no clinically significant extrapyramidal adverse effects - any time period[c], use of any antiparkinsonism drugs, other important adverse events Leaving the study early Service outcomes: admitted, number of admissions, length of hospitalisation, contacts with psychiatric services Compliance with drugs Economic evaluations: cost-effectiveness, cost-benefit General state: relapse, frequency and intensity of minor and major exacerbations Social confidence, social inclusion, social networks, or personalised quality of life: binary measure Distress among relatives: binary measure Burden on family: binary measure
Notes	[a]This could be diagnosed by clinical decision. If funds were permitting all participants could be screened using operational criteria, otherwise a random sample should suffice. [b]Size of study with sufficient power to highlight about a 10% difference between groups for primary outcome. [c]Primary outcome. The same applies to the measure of primary outcome as for diagnosis. Not everyone may need to have operational criteria applied if clinical impression is proved to be accurate.

Table 1. Other Cochrane Reviews in this series

Interventions	Current reference (updates underway)
Anticholinergic medication	Soares-Weiser 1997; Soares 2000
Benzodiazepines	Bhoopathi 2006

Table 1. Other Cochrane Reviews in this series *(Continued)*

Calcium channel blockers	Essali 2011
Cholinergic medication	Tammenmaa 2002
Gamma-aminobutyric acid agonists	Alabed 2011
Miscellaneous treatments	Soares-Weiser 2003
Neuroleptic reduction and/or cessation and neuroleptics	This review
Non-neuroleptic catecholaminergic drugs	El-Sayeh 2006
Vitamin E	Soares-Weiser 2011

APPENDICES

Appendix 1. Previous methods

Methods

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. We included trials that were described as double-blind, but that did not mention whether the study was randomised, in a sensitivity analysis. If there was no substantive difference within primary outcomes (see 'Types of outcome measures') when these studies were added, then we included them in the final analysis. If there was a substantive difference, we used only clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

We included people with schizophrenia or any other serious mental illness, diagnosed by any criteria, irrespective of gender, age or nationality who required the use of neuroleptics for more than three months and who developed TD (diagnosed by any criteria) during neuroleptic treatment, and for whom the dose of neuroleptic medication had been stable for one month or more. A post hoc change was made to include studies that did not require neuroleptic medication to have been stable for one month prior to randomisation. We felt it important to include these studies as they will provide additional important information. However, these will be analysed separately, and thus will not change existing outcome data.

Types of interventions

1. Reduction or cessation of the dose of the above drugs compared with the continuation of standard dose of the same compound. For the purposes of this review, these trials were divided into those that aimed to reduce the total dosage of neuroleptic medication, for example reduced dose and intermittent dosage schedule studies, and those that cease neuroleptics (sometimes after variable periods of dose reduction).

2. Specific neuroleptic drugs proposed to have TD lessening qualities compared to placebo or no intervention. A post hoc decision was made to broaden this criteria to also include neuroleptic versus neuroleptic for the treatment of TD.

Types of outcome measures

Clinical efficacy was defined as an improvement in the symptoms of TD of more than 50% on any scale.

The outcomes of interest were:

1. Tardive dyskinesia changes:
1.1. The number of people per treatment group who did not show an improvement of more than 50% on any TD scale
1.2. The number of people per treatment group who did not show any improvement on any TD scale
1.3. The number of people per treatment group who deteriorated on any TD scale
1.4. Treatment group mean change (endpoint - baseline) on any TD scale

1.5 .Treatment group mean change endpoint on any TD scale

2. Global assessment:
2.1. The number of people per treatment group who were defined as relapsed (according to any definition)
2.2. Leaving the study early

3. Adverse effects:
3.1. The number of people per treatment group who had any adverse effect (other than deterioration of symptoms of TD or relapse)

When appropriate, the outcomes were grouped into time periods - short term (less than 6 weeks), medium term (between 6 weeks and 6 months) and long term (over 6 months). Clinical efficacy was defined as an improvement in the symptoms of TD of more than 50%, on any scale.

Primary outcomes

Secondary outcomes

Search methods for identification of studies

1. Electronic searching for update (July 2005).

1.1. We searched The Cochrane Schizophrenia Group's Trials Register (July 2005) using the phrase:

[((dyskine* or diskine*) in title, abstract, index terms of REFERENCE) or ((dyskine* in health care conditions of STUDY)]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

2. We electronically searched previous versions of the CSG library

2.1. We identified relevant randomised trials by searching several electronic databases (the Cochrane Schizophrenia Group's Register of trials), Biological Abstracts, EMBASE, LILACS, MEDLINE, PsycLIT and SCISEARCH).

2.2. We searched the The Cochrane Schizophrenia Group's Register using the following phrases:

[(dyskine*) and (*amitrex* or *deniban* or *socian* or *solian* or *sulanid* or *sulamid* or *zyprex* or *olanzapin* or *ziprasidone* or *zotepine* or *lodopin* or *nipolept* or *zopite* or *setous* or *majpin* or *cloza* or *leponex* or *71675-85-9* or *neuroleptic* or chlorpromazine* or chlorprothixene* or dogmatil* or droperidol* or flupenthixol* or fluperlapine* or fluphenazine* or flunarizine* or haloperidol* or lonidine* or loxapine* or molindone* or penfluridol* or perphenazine* or pimozide* or piperacetazine* or sulpiride* or thiopropazate* or thioridazine* or thiothixene* or trifluoperazine* or clozapine* or zuclopenthixol* or risperidone* or pericyazine in title) or (*reduction* or *cessation* or *withdrawal* or *decrease* or *intermittent* or *target*) and (dyskine*)] and (*amitrex* or *deniban* or *socian* or *solian* or *sulanid* or *sulamid* or *zyprex* or *olanzapin* or *ziprasidone* or *zotepine* or *lodopin* or *nipolept* or *zopite* or *setous* or *majpin* or *cloza* or *leponex* or *71675-85-9* or *neuroleptic* or *chlorpromazine* or *chlorprothixene* or *dogmatil* or *droperidol* or *flupenthixol* or *fluperlapine* or *fluphenazine* or *flunarizine* or *haloperidol* or *lonidine* or *loxapine* or *molindone* or *penfluridol* or *perphenazine* or *pimozide* or *piperacetazine* or *sulpiride* or *thiopropazate* or *thioridazine* or *thiothixene* or *trifluoperazine* or *clozapine* or *zuclopenthixol* or *risperidone* or *pericyazine in title, abstract, index terms of REFERENCE) or ((antipsychotics or Targeted Medication* or Treatment Frequency* or Withdrawal* or Dosage of Drug* in interventions of STUDY) and (tardive in health care conditions of STUDY)]

[(dyskine* or #30 = 28) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine or #42 = 500)]

[(reduction or cessation or withdrawal or decrease or intermittent or target*) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

2.3. We searched BIOLOGICAL ABSTRACTS (January 1982 to September 1997) using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with each of the two phrases:

[and ((tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*)) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

[and (reduction or cessation or withdrawal or decrease or intermittent or target*) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

2.4. We searched EMBASE (January 1980 to September 1997) using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with each of the two phrases:

[and ((tardive dyskinesia in thesaurus -subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive or dyskines*) or (movement* or disorder*) or (abnormal or movement* or disorder*)) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

[and (reduction or cessation or withdrawal or decrease or intermittent or target*) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

2.5. We searched LILACS (January 1982 to September 1996) using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with each of the two phrases:

[and ((tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus)) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

[and (reduction or cessation or withdrawal or decrease or intermittent or target*) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

2.6. We searched MEDLINE (January 1966 to September 1997) using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with each of the two phrases:

[and ((movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and (psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*)) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

[and (reduction or cessation or withdrawal or decrease or intermittent or target*) and (antipsychotic-agents / all subheadings or neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

2.7. We searched PsycLIT (January 1974 to September 1997) using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with each of the two phrases:

[and ((explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*)) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

[and (reduction or cessation or withdrawal or decrease or intermittent or target*) and (neuroleptic* or chlorpromazine or chlorprothixene or dogmatil or droperidol or flupenthixol or fluperlapine or fluphenazine or flunarizine or haloperidol or lonidine or loxapine or molindone or penfluridol or perphenazine or pimozide or piperacetazine or sulpiride or thiopropazate or thioridazine or thiothixene or trifluoperazine or clozapine or zuclopenthixol or risperidone or pericyazine)]

3. Reference searching
3.1. SCISEARCH - Science Citation Index

We sought each of the included studies as a citation on the SCISEARCH database. We inspected reports of articles that had been cited from these studies in order to identify further trials.

3.2. We inspected the references of all identified studies for more studies.

4. Personal contact
We contacted the first author of each included study for information regarding unpublished trials.

Electronic searches

Searching other resources

Data collection and analysis

[For definitions of terms used in this, and other sections, please refer to the Glossary].

1. Selection of trials
We (KSW and JR) independently inspected citations from the searches and identified relevant abstracts. Where doubts arose, we acquired the full report for more detailed scrutiny. We obtained the full report of the abstracts that met the review criteria. Again, when resolving disputes by discussion was not possible, the article was added to those awaiting assessments and we contacted the authors of the study for clarification.

2. Assessment of methodological quality
KSW allocated trials to three quality criteria as described in the Cochrane Collaboration Handbook (Higgins 2005) and only trials meeting category A or B were included. In addition, we rated trials using the Jadad Scale (Jadad 1996) with a cut-off of two points used to check the assessment made by the handbook criteria. However, the latter were not used to exclude trials in this review.

3. Data management
3.1. Data extraction
We (KSW and JR) independently extracted data from included studies. Again, any disagreements were discussed, the decisions documented and, where necessary, we contacted the authors of the studies for clarification. Justifications for excluding references from the review were documented. We anticipated that many trials would have inadequate reporting and therefore, for those who dropped out of studies, we assumed they had no change in their TD symptoms. When insufficient data were provided to identify the original group size (prior to drop outs), we contacted the authors and the trials were allocated to the list of those awaiting assessment.

3.2. Intention to treat analysis
We excluded data from studies where more than 50% of participants in any group were lost to follow up (this does not include the outcome of 'leaving the study early'). In studies with less than 50% dropout rate, people leaving early were considered to have had the negative outcome, except for the event of death.

3.3. Dichotomous yes/no - data
We analysed dichotomous outcomes by calculating the relative risk (RR) (Fixed effects) with a 95% confidence interval (CI) to express the uncertainty of each result. The relative risk ratios from the individual trials were combined using appropriate methods of meta-analysis. When overall results were significant, the number needed to treat (NNT) to produce (or prevent) one outcome was calculated by combining the overall (RR) with an estimate of the prevalence of the event in the control groups of the trials. If heterogeneity was found (see section 5) we used a random effects model.

3.4 Continuous data
3.4.1. Skewed data: continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, the following standards were applied to all data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a scale started from the finite number zero, the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); (c) if a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied to them. When continuous data are presented on a scale which includes a possibility of negative values (such as change on a scale), it is difficult to tell whether data are non-normally distributed (skewed) or not.

For change data (endpoint minus baseline), the situation is even more problematic. In the absence of individual patient data it is impossible to know if data are skewed, though this is likely. After consulting the ALLSTAT electronic statistics mailing list, we presented change data in MetaView in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analyses could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Where both change and endpoint data were available for the same outcome category, we only presented endpoint data. We acknowledge that by doing this much of the published change data were excluded, but argue that endpoint data is more clinically relevant and that if change data were to

be presented along with endpoint data, it would be given undeserved equal prominence. We are contacting authors of studies reporting only change data for endpoint figures. Non-normally distributed data were reported in the 'other data types' tables.

3.4.2. Rating Scales
A wide range of instruments are available to measure outcomes in mental health studies. These instruments vary in quality and many are not validated, or are even ad hoc. As a minimum standard, we did not include data from an instrument in this review unless the instrument and its properties had been published in a peer-reviewed journal. In addition, the following minimum standards for instruments were set: The instrument should either be (a) a self-report or (b) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

3.4.3. Intention to treat analysis
Where possible we analysed data on an intention-to-treat basis and assumed that those who had not been accounted for had the negative outcome e.g. global assessment 'not improved' and relapse. This rule did not include the outcomes death or adverse effects. We tested this assumption with a sensitivity analysis. For continuous data it is impossible to manage the data in this way therefore we presented 'completer' data. Where feasible, we converted continuous scores to dichotomous data.

If, for a given outcome, more than 50% of the total numbers randomised were not accounted for, we did not present the results (except for leaving the study early) as such data are impossible to interpret with authority. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked data with '*' to indicate that the result may well be prone to bias.

4. Cluster trials
Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

5. Investigation for heterogeneity

Firstly, we considered all the included studies within any comparison to judge clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. This was supplemented, primarily, by employing the I-squared statistic. This provides an estimate of the percentage of inconsistency thought to be due to chance. Where the I-squared estimate was greater than or equal to 75%, this was interpreted as evidence of high levels of heterogeneity (Higgins 2003). Data were then re-analysed using a random effects model to see if this made a substantial difference. If it did, and results became more consistent, i.e. falling below 75% in the estimate, the studies were added to the main body of trials. If using the random effects model did not make a difference and inconsistency remained high, data were not summated, but were presented separately and reasons for heterogeneity investigated.

6. Addressing publication bias
We used funnel plots (trial effect versus trial size) for outcomes where more than five trials reported usable data, and visually inspected for asymmetry in an attempt to investigate the likelihood of overt publication bias (Egger 1997).

F E E D B A C K

Methods and results

Summary

This comment highlights the inconsistencies in the exclusion of studies in the review. In the 'Methods of the review' section some low-quality trials are excluded but they are included in the 'Results' section.

Reply

The review identified a marked lack of RCT-derived data. Informative data below RCTs in the hierarchy of evidence were identified from other trials. We chose to briefly mention these data in the discussion, but clearly identify that these trials could not be included in the study. We feel that this would help the clinicians in the absence of better data.

Contributors

Comment received from Ole Olsen, Copenhagen, September 1998
Reply from John McGrath, Brisbane, October 1999

WHAT'S NEW

Date	Event	Description
4 October 2017	New citation required and conclusions have changed	Results from latest searches do not change overall conclusions of this review
26 April 2017	New search has been performed	Update search run 26 April, 2017. Eight records found and assessed by editorial base Cochrane Schizophrenia, no new studies relevant to this review found. The 8 records were added to Studies awaiting classification of Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Table 1).
25 October 2016	Amended	Title changed from 'Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for neuroleptic-induced tardive dyskinesia'. Eight new trials added (Bai 2003; Bai 2005; Caroff 2011; Chan 2010; Chouinard 1995; Kazamatsuri 1973; Lublin 1991; Tamminga 1994), analyses and text updated, conclusions not substantially changed.

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 2, 1998

Date	Event	Description
16 July 2015	Amended	Update search run July 16, 2015. 704 records found and assessed by review authors.
26 April 2008	Amended	Converted to new review format.
20 September 2005	New citation required and conclusions have changed	Substantive amendment
25 February 1998	New search has been performed	Review first published
2 June 1997	New search has been performed	Protocol first published

CONTRIBUTIONS OF AUTHORS

HB - study selection, data extraction and assimilation, GRADE and Summary of Findings tables, report writing (2017 update)

JR - study selection, data extraction and assimilation, report writing (original version).

VA - report writing (2017 update).

KSW - protocol development, searching, study selection, data extraction and assimilation, report writing (original version and 2017 update).

DECLARATIONS OF INTEREST

HB worked for Enhance Reviews Ltd. during preparation of this review and was paid for her contribution to this review. Enhance Reviews Ltd. is a private company that performs systematic reviews of literature. HB works for Cochrane Response, an evidence consultancy that takes commissions from healthcare guideline developers and policy makers.

JR is not aware of any conflicts of interest for this review.

VA has declared no known conflicts of interest for this review.

KSW is the Deputy Editor-in-Chief for Cochrane and Cochrane Innovations. When the NHIR HTA programme grant relevant to this review update was awarded, KSW was the Managing Director of Enhance Reviews Ltd.

One of the earlier reviewers (JJM) is a member of the following advisory boards: Janssen-Cilag Australia, Eli Lilly Australia, Lundbeck Australia. In addition, JJM has been a co-investigator on studies of neuroleptic medications produced by the following companies: Astra Zeneca (ICI), Janssen-Cilag, Eli Lilly, Sandoz, and Pfizer. The same companies have provided travel and accommodation expenses for JJM to attend relevant investigator meetings and scientific symposia. No funds have been paid directly to JJM. Payments related to participation in drug trials and board attendance has been paid to a Government-audited trust account to support schizophrenia research.

SOURCES OF SUPPORT

Internal sources

- Queensland Health, Australia.
- CAPES - Ministry of Education, Brazil.
- Universidade Federal de São Paulo, Brazil.
- Enhance Reviews Ltd., UK.

  Logistics support for Hanna Bergman

External sources

- NIHR HTA Project Grant, reference number: 14/27/02, UK.

  Salary support for Hanna Bergman.
  Support for patient involvement consultation.
  Support for accessible, traceable data.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol as published with this review has evolved over time. The revisions of protocol are in line with the development of Review Manager and in keeping with Cochrane guidance. We think the revisions have greatly improved and enhanced this review. We do not think, however, that it has materially affected our conduct of the review or interpretation of the results.

There was a substantial update to the protocol in the 2017 review update. The biggest changes to affect the review were to:

1. broaden the inclusion criteria, and add the comparison 'Specific antipsychotic versus other drug';
2. change the title from 'Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia' to 'Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia';
3. update list of outcomes following consultation with consumers; and
4. add 'Summary of findings' tables.

Previous methods are reproduced in Appendix 1.

NOTES

Cochrane Schizophrenia Group internal peer review complete (see Group's Module).
External peer review scheduled.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*administration & dosage] [*adverse effects]; Dose-Response Relationship, Drug; Drug Administration Schedule; Drug Substitution; Dyskinesia, Drug-Induced [*drug therapy] [prevention & control]; Mental Disorders [drug therapy]; Randomized Controlled Trials as Topic; Schizophrenia [drug therapy]; Withholding Treatment

MeSH check words

Female; Humans; Male; Middle Aged